

**CHAPTER 56—DRUG QUALITY ASSURANCE**

<p><b>SUBJECT:</b> Surveillance Inspections of Protein Drug Substance Manufacturers</p> <p><b>REVISION:</b> This revision limits the scope of this compliance program to surveillance inspections and aligns with the Center for Drug Evaluation and Research (CDER) and Office of Regulatory Affairs (ORA) agreement <i>Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations (ConOps)</i>.</p>		<p><b>IMPLEMENTATION DATE:</b> October 1, 2021</p>
<b>DATA REPORTING</b>		
<b>PRODUCT CODE</b>	<b>PRODUCT/ASSIGNMENT CODE</b>	
<p>Profile Class Code: CBI Recombinant/Non-Recombinant Protein DS of Biologic Origin</p>	<p>Domestic/Foreign Inspections: 56002M Biotech Surveillance DS inspection</p>	

**FIELD REPORTING REQUIREMENTS:**

This compliance program<sup>1</sup> covers routine current good manufacturing practice (CGMP) inspections of manufacturers of drug substances (DS) regulated by CDER that meet the definition of *protein* as defined in 21 CFR 600.3(h)(6) (hereinafter *protein DS*).<sup>2</sup> The majority of the inspection reporting requirements described in this compliance program are standard reporting requirements for drug CGMP inspections; however, there are additional reporting requirements in Part III—Inspectional—and Attachments A, B, and C specific to protein DS manufacturing CGMP inspections.

If an inspection team obtains information during an inspection pertaining to inadequate adverse drug experience reporting, unapproved drug issues, or postapproval reporting violations (e.g., failing to submit application supplements, biological product deviation reports (BPDRs)), or the team observes adverse findings pertinent to the quality information provided in the site dossier, the inspection team should notify the Office of Quality Surveillance (OQS), in CDER’s Office of Pharmaceutical Quality (OPQ), in a timely manner by emailing [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc’ing [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov). Notifications should include a summary of the findings and any unreported changes the team believes should have been submitted to FDA per 21 CFR 601.12 (i.e., an annual reportable change, a change being effected supplement, or a prior approval supplement). The inspection team may refer to Part III.3.E—[Change Management and Reporting](#)—for additional information on protein DS manufacturing changes.

<sup>1</sup> *Compliance programs*, which were previously identified as *compliance program guidance manuals*, are available at <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/compliance-program-guidance-manual-cpgm>.

<sup>2</sup> See Part I.1—[Scope](#)—for additional information.

The applicable division within ORA completes the establishment inspection report (EIR) within ORA established time frames. No later than 45 calendar days from the close of the inspection, the EIR, exhibits, and attachments should be uploaded electronically using eNSpect. For Official Action Indicated (OAI) inspections, the ORA division submits advisory, administrative, or judicial action recommendations via Compliance Management Services (CMS).

ORA divisions should update Panorama and eNSpect in a timely manner when a potential OAI (pOAI) action is indicated.

ORA divisions (e.g., preapproval program managers (PAMs)) are responsible for timely entering of pOAI alerts in Panorama as per the current procedures. The PAM should consider the following when entering a pOAI alert into Panorama:

1. For surveillance coverage that may result in an OAI status, enter a pOAI alert in Panorama, as soon as practical, but at most within 2 days of closing the inspection.
2. Enter a pOAI alert for the refusal of an inspection.
3. If surveillance and preapproval coverage are provided during the same inspection:
  - a. Do not enter a pOAI alert for significant application-specific preapproval issues that do not impact marketed product; refer to compliance program 7346.832—*Preapproval Inspections*.
  - b. Do enter a pOAI alert for significant surveillance issues (see point 1).

The PAM must remove the pOAI alert in Panorama as soon as practical if the ORA division decides to change the initial pOAI recommendation. If the Office of Manufacturing Quality (OMQ), in CDER's Office of Compliance, decides not to maintain the initial pOAI recommendation, OMQ must update or remove the pOAI alert associated with that initial classification in Panorama as soon as practical. If OMQ concurs with the pOAI recommendation, OMQ should update the pOAI alert to an OAI alert.

In some cases, a surveillance inspection will include coverage of a for-cause assignment. In these cases, refer all EIRs (whether classified as No Action Indicated (NAI), Voluntary Action Indicated (VAI), or OAI) to CDER for OMQ review.

When the inspection team obtains information pertaining to inadequate adverse drug experience reporting, unapproved drug issues, or postapproval reporting violations (e.g., failing to submit application supplements, BPDRs), they should report the findings in accordance with directions provided in the applicable compliance programs, under separate captions in the EIR. Information about these inspectional activities should be reported in the Field Accomplishments and Compliance Tracking System (FACTS), eNSpect, or other data systems as required, using separate product/assignment codes (PACs).

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## PART I—BACKGROUND

### 1. Scope

This compliance program applies to current good manufacturing practice (CGMP) inspections of manufacturers of protein drug substances (DS)<sup>3</sup> regulated by the Center for Drug Evaluation and Research (CDER). In effect, this compliance program covers DS for CDER-regulated products that (1) meet the definition of *protein* as defined in 21 CFR 600.3(h)(6), which are *biological products* as defined by and licensed under section 351 of the Public Health Service (PHS) Act,<sup>4</sup> and (2) are manufactured using biotechnology processes (e.g., recombinant protein technology).

Examples of these products include, but are not limited to:

- Enzymes.
- Monoclonal antibodies.
- Antibody-drug conjugates.
- Fusion proteins (e.g., antibody Fc region-containing fusion proteins).
- Growth factors.
- Cytokines (e.g., interleukins, interferons, tumor necrosis factors).
- Botulinum toxins.

Email questions regarding whether a product is covered by this compliance program to [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc: [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov).

This compliance program does **not** apply to:

- Biological product fill/finish operations. Inspections of these operations are conducted under compliance program 7356.002A—*Sterile Drug Process Inspections*.
- Biological products with protein DS that are manufactured by chemical synthesis. Inspection of facilities that manufacture these protein DSs are conducted under compliance program 7356.002F—*Active Pharmaceutical Ingredient (API) Process Inspection*.
- Antibiotics and other small-molecule APIs produced by microbial fermentation. Inspections of facilities that manufacture these antibiotics and other small-molecule APIs are conducted under compliance program 7356.002F.

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<sup>3</sup> In this compliance program, unless specified otherwise, the terms *drug substance* and *active pharmaceutical ingredient* (or *API*) are used interchangeably.

<sup>4</sup> The Biologics Price Competition and Innovation (BPCI) Act of 2009 amended the PHS Act (42 U.S.C. 262) to add section 351(k), creating an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, a biological reference product licensed under section 351(a) of the PHS Act (see sections 7001 through 7003 of the Patient Protection and Affordable Care Act, Pub. L. 111-148).

## 2. Program Approach—Risk-Based Inspectional Coverage

This compliance program is organized according to the pharmaceutical manufacturing systems described in compliance program 7356.002—*Drug Manufacturing Inspections*. Part III of this compliance program provides background information for each system in the context of a protein DS manufacturing establishment.<sup>5</sup> Attachment A contains questions related to each system that provide focus for the inspectional coverage, targeting areas where deficiencies may significantly impact product quality.

## 3. Applicable Statutes, Regulations, and Guidance

Under section 501 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), all drugs,<sup>6</sup> including biological products, must be manufactured in accordance with CGMP requirements or otherwise be considered adulterated.<sup>7</sup> Biological products licensed under the provisions of section 351 of the PHS Act must comply with the applicable regulations in 21 CFR parts 600, 601, and 610.<sup>8</sup>

FDA's current thinking on CGMP for protein DS can be found in FDA's International Council for Harmonisation (ICH) guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016).<sup>9</sup> The inspection team should be familiar with section XVIII of ICH Q7, Specific Guidance for APIs Manufactured by Cell Culture/Fermentation; it is applicable to many of the protein DS and manufacturing operations

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<sup>5</sup> Throughout the rest of this compliance program, *establishment* refers to manufacturing establishments (see 21 CFR 600.3(w)).

<sup>6</sup> Per section 201: "The term 'drug' means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)."

<sup>7</sup> Per section 501: "A drug or device shall be deemed to be adulterated if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." As amended by section 711 of the Food and Drug Administration Safety and Innovation Act (2012) (Pub. L. 112-144), "the term 'current good manufacturing practice' includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."

<sup>8</sup> Specified categories of biological products (often referred to as *specified biotech*), defined in 21 CFR 601.2, are exempted from complying with certain biologics regulations.

<sup>9</sup> Throughout this compliance program, *guidance for industry*, *ICH guidance for industry* (including subsequent *ICH Q#* references), and *guide to inspections* refer to FDA documents. 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>.



covered by this compliance program. ICH Q7 does not establish mandatory requirements but does describe generally accepted minimum standards. If uncertain regarding whether ICH Q7 is appropriate for the specific manufacturing or testing operations covered on inspection, inspection teams are encouraged to contact experts in the Office of Regulatory Affairs (ORA) or CDER for clarification.

#### 4. General Overview of Protein DS Manufacturing Processes

In general, the protein DS manufacturing process can be divided into stages:

1. Cell Banking
  - a. Protein DS may be expressed, extracted, and purified from various sources, including the milk and eggs of transgenic animals and the leaves and fruits of transgenic plants. However, in most cases, the desired protein is expressed, recovered, and purified from cell culture/fermentation.
  - b. Mammalian and bacterial cell lines are the most commonly used expression systems, but yeast or plant cell lines can be used.
  - c. Once the expression cell line has been chosen, the manufacturer establishes a master cell bank (MCB), which is a collection of ampoules/vials containing aliquoted cells derived from a single cell or colony, expressing the protein of interest. The MCB should be stored under defined, validated conditions.
  - d. In general, from an MCB vial, the manufacturer creates a working cell bank (WCB), which is used to initiate every production run.
2. Upstream Manufacturing (Cell Growth and Crude Protein Harvest)
  - a. Cells from a WCB vial are expanded, in the appropriate medium, by passing them into increasingly larger vessels until the cells reach an established density.
  - b. The expanded cell culture is transferred to a production-scale fermenter/bioreactor to continue a controlled cell growth and protein expression for a predetermined length of time. Cell culture expansion stages are designed with stringent controls to prevent adventitious microorganism introduction, proliferation, or persistence.
  - c. When the cell culture/fermentation process is complete, the unpurified protein DS is harvested and clarified from the cell culture/fermentation broth using steps such as centrifugation, depth filtration, and ultrafiltration/diafiltration (UF/DF) to remove cells and cell debris.

If the protein is not secreted into the growth medium (i.e., it remains intracellular), the cells are collected and subjected to lytic enzymes or physical treatments such as homogenization to release the protein.

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3. Downstream Manufacturing (Purification and Formulation)
    - a. Purification may include precipitation, UF/DF, affinity column chromatography, and traditional column chromatography (e.g., anion exchange chromatography).
    - b. Purification steps are designed to separate the protein of interest from process- and product-related impurities, such as media components, host cell proteins, and DNA, and to target for removal protein that is aggregated, misfolded, or truncated.
    - c. Depending on the host expression system, there may be steps to inactivate or clear adventitious agents (e.g., viruses), which include, but are not limited to, detergent inactivation, low pH hold, viral filtration, and heat treatment.
    - d. There may be steps designed to concentrate the protein DS or perform buffer exchanges.
    - e. In general, at the end of the purification process, the purified protein DS is formulated and bulk-filled for shipment to a drug product fill/finish establishment.

## PART II—IMPLEMENTATION

### 1. Objectives

This compliance program provides information and guidance to inspection teams and supervisors/compliance officers (COs) assigned to conduct and review, respectively, CGMP surveillance inspections of protein DS manufacturers.

Inspections under this compliance program focus on:

- Monitoring firms' conformance to CGMP requirements (e.g., determining whether their manufacturing operations consistently produce protein DSs for products to be safe, pure, and potent).<sup>10</sup>
- Providing an assessment of firms' conformance to CGMP requirements for FDA decisions.
- Providing input to firms (e.g., discussing compendial references, the preamble to regulations, or current guidance for industry) during inspections to improve their compliance with regulations.
- Acquiring a better understanding of current practices in drug manufacturing for the purpose of updating CGMP requirements, regulatory policy, and guidance documents. This includes identifying quality problems and adverse trends so that FDA can develop strategies to mitigate them.

If deficiencies are found in an establishment's manufacturing operations, this compliance program:

- Encourages, if applicable, voluntary compliance by (1) identifying specific practices that need correction or improvement, and (2) identifying systems and programs that need to be established or improved.
- Provides regulatory/administrative instructions to FDA personnel (Part V), including the collection of evidence, to ensure that adulterated product does not enter the market or is removed from the market and that appropriate actions are initiated against those manufacturers found to be in significant noncompliance with applicable laws and regulations.

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<sup>10</sup> The inspection team is also expected to evaluate which changes have been introduced to the manufacturing processes conducted in the establishment and whether these changes were appropriately reported to and, if applicable, approved by FDA.

## 2. Program Management Instructions

### A. Strategy—Systems-Based Inspections Accentuating Highest Risk Areas

Inspectional coverage under this compliance program is arranged in accordance with the six pharmaceutical manufacturing systems described in compliance program 7356.002: quality, facilities and equipment, materials, production, laboratory control, and packaging and labeling. All six systems (in the context of a protein DS establishment) contain at least one area of sufficiently high risk to justify routine coverage. Therefore, each pharmaceutical manufacturing system should be covered adequately on each surveillance inspection of protein DS manufacturers, with emphasis on areas of highest risk. No abbreviated surveillance inspection is permitted under this compliance program.

### B. Inspection Planning

#### (1) OQS Inspection Assignments

The Office of Quality Surveillance (OQS), in CDER's Office of Pharmaceutical Quality (OPQ), develops and uses a risk-based site selection model to assess the relative quality risk for facilities in the manufacturing facility catalog.<sup>11</sup> This model generates a risk-based ranking of sites to annually prioritize inspections. The risk factors used in the model are as detailed in section 704 of the FD&C Act and include, but are not limited to, the compliance history of the establishment; the records, history, and nature of recalls; the inherent risk of the drugs at the site; the inspection frequency and history of the site; whether the site has been inspected by a foreign regulatory authority; and other criteria deemed necessary by the Secretary of the U.S. Department of Health and Human Services for purposes of allocating inspection resources. After CDER selects sites for inspection, ORA schedules the inspections.

#### (2) OQS Site Dossier

The ORA consumer safety officer (CSO), supervisory CSO, or district preapproval program manager should email a request for a site dossier to [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov) as soon as an inspection is scheduled. After receiving the request, and in advance of the scheduled inspection, OQS prepares the dossier that includes, but is not limited to, the following information:

- Site inspection history.
- Recalls, drug shortage concerns, MedWatch reports, and customer complaints for protein DS or CDER-regulated products manufactured at the site.
- Foreign regulator inspection outcomes.
- Information submitted in BPDRs.

<sup>11</sup> See MAPP 5014.1 *Understanding CDER's Risk-Based Site Selection Model*, available at <https://www.fda.gov/media/118214/download>.

- Quality management maturity information, including quality metric data, if available.
- List of CDER-regulated products manufactured at the site and, where applicable, approved established conditions.<sup>12</sup>
- CDER product specialists' contact information.

The site dossier helps the inspection team develop an inspection plan with a focus on areas likely to have the highest impact on product quality and, ultimately, clinical outcome.

### (3) Inspection Team

ORA leads surveillance facility inspections with CDER participation, when requested by ORA or when requested by CDER and agreed upon by ORA. ORA should email [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc: [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov) as early as possible to request CDER participation before the start of the inspection. For domestic and foreign inspections, CDER needs approximately 45 and 75 days, respectively, for travel arrangements. If a CDER product specialist does not participate, an additional ORA investigator or analyst may accompany the lead investigator. For the products covered by this compliance program, the CDER product specialists are from OPQ. The size and composition of the inspection team should be informed by factors such as the volume and complexity of products manufactured, the type and extent of deficiencies identified on previous inspections, and the composition of recent inspection teams. If a microbiologist with expertise in protein manufacturing has not participated in either of the two most recent establishment surveillance inspections to the site, every effort should be made to include one from ORA or CDER. The inspection team may include ORA and CDER trainees to achieve FDA training objectives.

### (4) Inspection Duration

If planning a protein DS surveillance inspection to be conducted concurrently with other surveillance coverage, such as coverage of small molecule APIs or drug product manufacturing operations, some aspects of surveillance coverage may meet the objectives of multiple compliance programs simultaneously. However, there are aspects of coverage **specific to this compliance program** not addressed by other programs. These aspects are expected to be met when reporting surveillance coverage under this compliance program; therefore, this expectation should inform the planned inspection duration.

Because the inspection team is expected to thoroughly evaluate the corrective actions and preventive actions (CAPAs) that the manufacturer has implemented to address Form FDA 483 (hereinafter *483*) observations cited in the most recent inspection(s), the time needed to perform this activity should be considered when determining inspection duration. This is true particularly if the recent 483 observations were extensive.

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<sup>12</sup> See ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021) and Part III.3.E—[Change Management and Reporting](#).

Each protein DS manufactured at the establishment should be afforded enough coverage to determine, with sufficient confidence, that manufacturing activities are in a state of control and supported by a robust pharmaceutical quality system (PQS).<sup>13</sup>

### C. Profile Reporting

Only one profile should be updated as a result of coverage specified under this compliance program. The relevant Field Accomplishments and Compliance Tracking System (FACTS) profile class code for protein DS regulated by CDER is CBI (Recombinant/Non-Recombinant Protein DS of Biologic Origin). For more information, see exhibit 5-14 Profiling a Firm's CGMP/QS Compliance Status in the *Investigations Operations Manual*.

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<sup>13</sup> The PQS is a management system to direct and control a pharmaceutical company with regard to quality (see ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) recommendation PI 054-1 *How To Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management* (July 2021), <https://picscheme.org/docview/4294>).

## PART III—INSPECTIONAL

### 1. Reporting

In preparing the inspection report, the inspection team should follow instructions in compliance program 7356.002, the *Investigations Operations Manual* (chapter 5), and the *Guide to International Inspections and Travel*. In the “Manufacturing/Design Operations” section of the inspection report, the inspection team should summarize its findings for the six pharmaceutical manufacturing systems described in compliance program 7356.002 in accordance with the key elements outlined below, with sufficient details and supporting evidence for each 483 observation.

### 2. Inspectional Coverage

#### A. Coverage of All Six Pharmaceutical Manufacturing Systems

There is no abbreviated inspection option for inspections conducted under this compliance program, which requires substantial coverage of all six pharmaceutical manufacturing systems.

Part III of this compliance program provides background information for each system in the context of protein DS manufacturing and includes links to the Attachment A questions that help the inspection team cover the most essential aspects of each system (i.e., highest risk areas in protein DS facilities).

#### B. OQS Site Dossier

During the inspection, the inspection team should assess areas identified as highest risk in the OQS site dossier. The site dossier is intended to inform the inspection team about issues specific to the protein DS facility to be inspected (e.g., issues with, or recent changes to, critical materials, processes, or test methods).

### 3. Quality System

As described in compliance program 7356.002, there are two major objectives to meet when inspecting the quality system. The first objective is to assess whether the quality unit has fulfilled its responsibility to review and approve **suitable** production, quality control, and quality assurance procedures. The second is to identify potential product quality issues by reviewing production and testing records, data summaries, and relevant evaluations of control.

Given the complexity of protein DS manufacturing, a comprehensive review of raw materials, production processes, testing methods, and investigation records should be completed when inspecting the quality system. The inspection team should, with high confidence, make sure that the quality system is able to detect potential quality issues and respond appropriately. This

includes determining whether the manufacturing process has remained within a state of control and whether the firm has taken the appropriate steps to regain control if necessary.

To ensure the implementation of an effective PQS and to formalize their quality risk management programs, manufacturers may conduct operations, in whole or in part, consistent with recommendations in the guidance documents listed below. Most of the concepts discussed in these documents are particularly applicable to protein DS manufacturers and consistent with CGMP expectations. Therefore, the inspection team should be familiar with these documents to facilitate quality system inspectional coverage:

- ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients: Questions and Answers* (April 2018).
- ICH guidance for industry *Q9 Quality Risk Management* (June 2006).
- ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009).
- ICH guidance for industry *Q8, Q9, and Q10 Questions and Answers(R4)* (November 2011).
- ICH guidance for industry *Q8, Q9, and Q10 Questions and Answers—Appendix: Q&As From Training Sessions (Points to Consider for Q8, Q9, & Q10)* (July 2012).
- ICH guidance for industry *Q11 Development and Manufacture of Drug Substances* (November 2012).
- ICH guidance for industry *Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Questions and Answers* (February 2018).
- ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021).
- Guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006).
- Draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021)<sup>14</sup>
- Pharmaceutical Inspection Co-operation Scheme (PIC/S) *How To Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management* (July 2021).

#### A. Senior Management Responsibility

This section applies to a firm's senior management—managers authorized to establish or make changes to the firm's quality management system.

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<sup>14</sup> When final, this guidance will represent FDA's current thinking on this topic.



Effective management oversight is essential for a well-functioning PQS. The inspection team should assess whether management is taking responsibility for this oversight. If the inspection team finds significant product quality issues or significant CGMP violations during an inspection, the team should cover/evaluate the questions related to senior management responsibility in Attachment A and should report this coverage/evaluation in the establishment inspection report (EIR) narrative. The inspection team should also assess how well the firm has integrated modern PQS concepts into its daily operations. Because this inspectional coverage may identify the root causes of quality issues or CGMP violations, it may inform FDA's regulatory strategy and post-inspection communication with the firm.

Reference: ICH Q10, section III, Management Responsibility

See Attachment A—[Senior Management Responsibility](#)—for pertinent questions.

#### B. Quality Unit

As with all drug manufacturers, protein DS manufacturers should have a quality unit that is involved in all quality-related matters and decisions. The quality unit reviews and approves all procedures related to production, quality control, and quality assurance and ensures that these procedures are adequate for their intended use. The quality unit also ensures that record keeping systems operate as intended.

**Special considerations for contract manufacturers:** FDA regulations recognize that applicants commonly use contract facilities to perform some drug manufacturing activities. When an applicant uses a contract facility, the applicant's quality unit is legally responsible for approving or rejecting drug products manufactured by the contract facility, including for final release. There should be a written and approved contract or formal agreement between the applicant and its contractors that defines in detail the CGMP responsibilities of each party, including the quality measures. In all cases, the inspection team should be particularly mindful to establish that the protein DS manufacturer's quality unit is meeting its regulatory responsibilities and **not**, inappropriately, deferring to the applicant's quality unit. Although the applicant's quality unit is ultimately responsible for approving or rejecting material produced by the contract manufacturer, the contract manufacturer is not absolved from its statutory requirement to manufacture in accordance with CGMP requirements. This includes, for example, conducting thorough and timely investigations into manufacturing and testing deviations, regardless of product disposition. Additionally, contract manufacturers should promptly notify applicants following such deviations and should make relevant records available to them.

Applicants and contract manufacturers should work together to establish and maintain appropriate quality oversight of contracted manufacturing operations. ICH Q10 recommends that owners and contractors define the responsibilities and communication processes for the quality-related activities of both parties and document these in a written agreement. Guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (November 2016) provides recommendations on the content of such agreements. Other types of cooperative manufacturing arrangements for protein products—shared and divided arrangements—are

discussed in guidance for industry *Cooperative Manufacturing Arrangements for Licensed Biologics* (November 2008).

Reference: ICH Q7, section II.B, Responsibilities of the Quality Unit(s)

See Attachment A—[Quality Unit](#)—for pertinent questions.

### C. Internal Audits

The firm should perform regular internal audits to confirm that its operations are in conformance with CGMP. The inspection team should confirm that the firm has a written quality assurance program that includes periodic auditing and critical review of processes and procedures to ensure they are being followed. However, as articulated in CPG Sec. 130.300 *FDA Access to Results of Quality Assurance Program Audits and Inspections*, the inspection team should not request internal audit results during the surveillance inspection.

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

See Attachment A—[Internal Audits](#)—for pertinent questions.

### D. Process Performance and Product Quality Monitoring

#### (1) Ongoing Program

The firm should have an ongoing program to monitor product quality and manufacturing process performance. The program should be capable of identifying both near- and long-term trends that could impact product quality and should include ongoing review of the following:

- Performance of manufacturing and analytical processes.
- Facility and equipment suitability and performance.
- Raw material variability.
- Quality attribute in-process monitoring and testing results.
- Release and stability testing results.
- Nonconformances, deviations, errors, and atypical events.
- Product quality failures, quality anomalies, and out-of-specification (OOS) results.
- Complaints, returns, and recalls.
- Regulatory findings (local, or at another site in the supply chain).
- Internal and external audits.
- Record authenticity (data integrity).

Evaluating the consistency of manufacturing processes is a critical aspect of quality monitoring. If evidence of inconsistency is found, the firm should promptly regain control. Inconsistencies and drift in protein DS manufacturing processes can directly impact product safety and efficacy by unintentionally altering the biochemical and biophysical properties of these products in ways that may not necessarily be identified by routine testing.

References:

- ICH Q10, section IV.B.1, Process Performance and Product Quality Monitoring System
- Guidance for industry *Process Validation: General Principles and Practices* (January 2011), section IV.D, Stage 3—Continued Process Verification
- Consensus standards offering specific statistical quality control tools:
  - ASTM E2281: Standard Practice for Process Capability and Performance Measurement
  - ASTM E2587: Standard Practice for Use of Control Charts in Statistical Process Control

See Attachment A—[Ongoing Program](#)—for pertinent questions.

## (2) Annual Review

In addition to its ongoing monitoring program, the firm should conduct and formally document, at least annually, a product quality review of each protein DS it manufactures. These reviews should include summary analyses of much of the data evaluated by the ongoing process performance and product quality monitoring program and should specifically cover, among other things, the following:

- Critical in-process control and release test results.\*
- Batches failing to meet established specifications.\*
- Critical deviations or nonconformances, OOS test results, and related investigations.\*
- Changes carried out to manufacturing processes or analytical methods.\*
- Stability monitoring program results.\*
- Quality-related complaints, returns, and recalls.\*
- The adequacy of implemented corrective actions.\*
- Process performance/capability.
- Trending of critical quality attributes.

\*Reference: ICH Q7, section II.E, Product Quality Review

The inspection team should evaluate recent product quality reviews for each protein DS manufactured at the establishment.

See Attachment A—[Annual Review](#)—for pertinent questions.

## E. Change Management and Reporting

Change management is a basic PQS element that involves evaluating, approving, and implementing changes throughout a product's lifecycle. Because of the complex relationship between the quality attributes of protein products and the characteristics of the manufacturing process of protein DS, the inspection team should assess whether protein DS manufacturers have

a robust change management system that evaluates manufacturing changes in a manner commensurate with the level of risk imposed by a proposed change.

Manufacturers of protein products, as described in 21 CFR 601.12, must inform FDA about changes to “the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s).” Some individual applicants have reached reporting agreements with FDA that define the type of reporting for certain changes following the principles outlined in ICH Q12. Such agreements are referred to as *established conditions* and are maintained, along with postapproval change management protocols (PACMPs, also referred to as comparability protocols), in the biologics license application (BLA) in the Product Lifecycle Management (PLCM) document.

If, after reviewing the PLCM document, there is any question as to the impact of a change on the protein DS, whether it should have been reported, or whether it should have been submitted in a supplement rather than an annual report, the inspection team should contact CDER by emailing [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc'ing [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov). The email will be triaged to the appropriate CDER assessor. **The inspection team should not request manufacturing supplements to be submitted unless CDER confirms that the submission is appropriate.**

If protein DS manufacturers introduce change, they should carefully manage it. Manufacturers should have a formal change management system with appropriately detailed written procedures. Most changes to processes, controls, materials, facilities, and equipment carry at least **some** risk of affecting the safety or efficacy of these products. Accordingly, **changes should be evaluated for potential product quality impact** and should be reviewed and approved by appropriate organizational units.

The inspection team should request a list of changes or modifications made to products, materials, processes, facilities, equipment, and quality controls since the last inspection. When deciding which change control documentation to review, the inspection team should consider focusing on changes with the highest likelihood to affect product quality. During its review, the inspection team should determine whether the changes were reported to CDER as appropriate.

If there is a PACMP, the inspection team should verify the implementation status of any change.

- Review that the change as implemented aligns with the relevant study protocols, PLCM document, or PACMP.
- Verify whether the data generated demonstrate that the change objective and acceptance criteria were met.

If there is a PLCM document, the inspection team should verify the maintenance status of the document in terms of when and how the document is updated.

- Review that the document was updated after the change was implemented to capture any new product/process knowledge gained during implementation.
- Verify whether any subsequent regulatory filings for the product have been included in the document.

General questions on change control are found in [Change Management and Reporting](#) in Attachment A; however, in areas warranting increased scrutiny, specific questions have also been included under the relevant system sections in Attachment A (e.g., [Materials System](#), [Production System](#)).

References:

- ICH Q7, section XIII, Change Control
- ICH Q12
- Guidance for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)
- Guidance for industry *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021)
- Draft guidance for industry *CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports* (August 2017)<sup>15</sup>
- Draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products*<sup>16</sup>

See Attachment A—[Change Management and Reporting](#)—for pertinent questions.

#### F. Validation and Verification Activities

Manufacturing and testing in conformance with CGMP requirements require validation activities; manufacturers should collect and evaluate data demonstrating that equipment, processes, and test methods are capable of consistently performing as intended **before** using those processes and methods to produce and test marketed products. Verification and validation activities are a primary point of focus for inspections of protein DS manufacturers supporting approval of a BLA; however, verification activities consistent with a lifecycle approach to validation, as well as any new validation activities, should be covered during routine surveillance inspections.

General coverage of the firm's validation programs/activities is included in the quality system section because the quality unit oversees these activities, including:

- Approving qualification/validation protocols and reports.
- Ensuring that the firm practices a lifecycle approach to validation activities and ensuring that effective verification and requalification efforts occur.
- Leading investigations into the failure of validated processes and test methods.

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<sup>15</sup> When final, this guidance will represent FDA's current thinking on this topic.

<sup>16</sup> Ibid.

- Leading new validation efforts if significant changes to existing processes and test methods are needed.

The inspection team should focus on validation/verification deviations or failures and should ensure that the firm has properly evaluated their impact on product quality. This is particularly true of deviations or failures affecting cell culture, fermentation and purification processes, viral clearance/inactivation, manufacturing equipment, and analytical test methods. General questions on validation and verification activities are found in Attachment A. Specific validation activities are covered in more detail in the following systems:

- Production system: The consistency of the manufacturing process, conformance with validated processes, and continuous process verification (see Part III.6.A(5)—[Process Validation](#)).
- Laboratory control system: The use of validated analytical test methods and the validation of new test methods (see Part III.7.A(5)—[Test Method Validation and Postapproval Changes](#)).
- Facilities and equipment system: The firm's program for equipment qualification and requalification as well as equipment cleaning and sanitization/sterilization (see Parts III.4.A(2)—[Equipment Qualification and Requalification](#), III.4.A(4)—[Equipment Cleaning](#), and III.4.A(5)—[Equipment Sanitization and Sterilization](#)).
- Packaging and labeling system: The shipment of the bulk protein DS to the drug product fill/finish establishment (see Part III.8—[Packaging and Labeling System](#)).

See Attachment A—[Validation and Verification Activities](#)—for pertinent questions.

#### G. Stability Program

The firm should have a program that demonstrates the continued stability of each protein DS it manufactures and that the DS batches meet approved specifications. In general, at least one batch of each manufactured protein DS should be subjected to stability testing annually, and the firm should consider subjecting additional batches if it encounters major deviations or anomalies during the manufacturing of those batches. However, additional testing should not be done merely to close out a deviation without attempting to establish a root cause. Stability test failures should be reported to FDA as appropriate.

Part III.7.A(7)—[Stability Testing and Reserve Samples](#)—provides additional information on stability testing, including several references.

Reference: ICH Q7, section XI.E, Stability Monitoring of APIs

See Attachment A—[Stability Program](#)—for pertinent questions.

## H. Deviation and Failure Investigations

A primary indicator of an establishment's state of control is its ability to conduct thorough and meaningful investigations with well-supported conclusions and relevant CAPAs in response to process and testing excursions, deviations, and failures.

The inspection team should review an appropriate number of deviation records (e.g., nonconformance, discrepancies, incidents) to evaluate the firm's quality system strategies of investigating, documenting, and resolving deviations and failures as well as associated CAPAs. General questions on deviation and failure investigations are linked to below, and questions on these investigations as they relate to specific high-risk areas are located throughout Attachment A.

Reference: ICH Q7, section II.A, Principles

See Attachment A—[Deviation and Failure Investigations](#)—for pertinent questions.

## I. Rejected/Aborted and Reprocessed Batches

The firm's quality unit should oversee investigations into rejected/aborted batches as well as reprocessing and reworking decisions.

Rejected and aborted batches of protein DS may indicate the firm has a problem with contamination events or production controls. The frequency of, and reason for, rejected and aborted batches may be investigated and documented by reconciling the number and dates when WCB aliquots were used for production or testing operations.

Reprocessing and reworking are covered in the production system section (see Part III.6.A(6)—[Reworking and Reprocessing](#)).

See Attachment A—[Rejected/Aborted and Reprocessed Batches](#)—for pertinent questions.

## J. Complaints and Adverse Experience Reports

Protein DS manufacturers may not have extensive complaint and adverse experience report (AER) records if they are not also responsible for end user complaint and AER management.<sup>17</sup> However, inspection teams should review records of complaints (internal and external), adverse experiences, and associated investigations as submitted to the firm by any establishment responsible for product complaint and AER management. If complaints or AERs are received by another establishment or company, the inspection team should verify that there are adequate procedures for proper reporting of complaints and adverse events among establishments within the company or among companies. Although end-user complaints and adverse events are often related to fill/finish operations, this does not preclude the possibility that some complaints or

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<sup>17</sup> 21 CFR 600.80 requires that serious, unexpected adverse experiences associated with the use (in humans) of a biological product licensed under a BLA be reported to FDA no later than 15 calendar days from initial information receipt by the licensed manufacturer, with follow-up reporting 15 calendar days thereafter or as requested by FDA.

adverse events are related to the quality of the protein DS. Therefore, the inspection team should focus on complaints or AERs that are potentially related to the quality of the protein DS, reviewing relevant investigations. Examples of relevant complaints may include those related to the appearance, shipping, or contamination of the protein DS. AERs potentially related to the quality of the protein DS could include those for lack of effect, increased immunogenicity, fever, and injection site reactions, among others. Because it may be difficult to determine the significance of any single AER, the inspection team should consider focusing on reports clustering around a specific protein DS batch or on significant increases in reporting (either as trended by the manufacturer or apparent from the inspection team's review of an AER list/summary).

If there are questions or concerns regarding the seriousness of, and hence the reporting requirements for, an adverse experience, the inspection team should email [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc: [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov).

Reference: ICH Q7, section XV, Complaints and Recalls

See Attachment A—[Complaints and Adverse Experience Reports](#)—for pertinent questions.

#### K. Returns

Returned protein DS should be identified and documented as returned and quarantined to prevent inappropriate use. Because protein DS should be shipped using validated processes, determining whether the protein DS has been handled appropriately or experienced any controlled environment excursions should be part of any disposition decision unless the returned DS has been or is scheduled to be destroyed. The return of protein DS should be a rare occurrence.

See Attachment A—[Returns](#)—for pertinent questions.

#### L. Drug Quality Reports—BPDRs

According to 21 CFR 600.14, BLA license holders (applicants) must send CDER a BPDR (Form FDA 3486) within 45 calendar days for unexpected or unforeseen events or deviations related to distributed products that may affect product safety, purity, or potency. Establishments that manufacture protein DS only (no product fill/finish operations) often are not the establishment responsible for submitting BPDRs; however, deviations or unexpected or unforeseen events that occur at the protein DS establishments may be reportable. At a minimum, the protein DS establishment should have a written procedure describing how reportable events are communicated to the party responsible for submitting BPDRs. If drug quality reporting is required because of a deviation at the protein DS establishment, but the protein DS manufacturer is unable to provide evidence that a BPDR was submitted to CDER, the inspection team should email [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc: [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov), providing the BLA number, finished product name, date when the reportable biological deviation was discovered, and establishment name and FDA establishment identifier (FEI) where the biological product deviation occurred. CDER will determine whether a report was filed. The inspection team should also collect the event/deviation report, a copy of the agreement between



the manufacturer and applicant regarding the communication of deviations, a copy of the postmarket reporting procedures, and evidence that the deviation was reported to the applicant.

See Attachment A—[Drug Quality Reports—BPDRs](#)—for pertinent questions.

#### M. Quarantined Protein DS

Protein DS batches that have not yet been released by the quality unit or are pending a disposition decision for any other reason (such as a return) should be placed in quarantine—segregated from released batches by physical or other effective controls to prevent their use until a disposition decision has been reached.

See Attachment A—[Quarantined Protein DS](#)—for pertinent questions.

#### N. Recalls

The firm should have a written procedure documenting the circumstances under which batch recall should be considered. The procedure should define the parties involved in the recall evaluation and describe how the recall should be initiated, who should be notified, and how the recalled material should be quarantined and dispositioned..

Reference: ICH Q7, section XV, Complaints and Recalls

See Attachment A—[Recalls](#)—for pertinent questions.

#### O. Data Integrity

Data integrity refers to the completeness, consistency, and accuracy of data, which should be attributable, legible, contemporaneously recorded, and either the original record or a true copy. The quality unit should ensure the integrity of records required to demonstrate CGMP compliance. The inspection team should cover all data integrity questions in Attachment A if the firm has not recently been inspected for appropriate record keeping practices and should speak with relevant IT system administrators to verify record keeping systems are validated and controlled for user permissions.

The inspection team should also consider covering the data integrity questions in Attachment A while reviewing the adequacy of production and laboratory records (see Parts III.6.A(2)—Master and Batch Production Records, and III.7.A(3)—Record Keeping).

References:

- Guidance for industry *Data Integrity and Compliance With Drug CGMP: Questions and Answers* (December 2018)
- Guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* (October 2006)

See Attachment A—[Data Integrity](#)—for pertinent questions.

#### 4. Facilities and Equipment System

All manufacturers should have suitable equipment and facilities to ensure the quality of the drugs they produce.

Manufacturers of protein DS qualify and maintain several pieces of critical equipment not typically seen at other types of establishments, including fermenters/bioreactors, centrifuges, depth filtration equipment, UF/DF equipment, and column chromatography equipment. Although qualification activities associated with using this equipment are typically assessed before application approval, the inspection team needs to assess the firm's verification activities related to equipment maintenance and requalification/continued performance as well as the qualification of new pieces of equipment.

Although not necessarily unique to protein DS manufacturers, several utilities generally found in these manufacturing facilities should be maintained and requalified as appropriate. Utilities include water for injection (WFI) and purified water systems, process gas systems, and clean steam systems. Maintaining WFI and purified water systems is particularly important because water is a critical material for biotechnological manufacturing and large volumes of it must be generated.

The inspection team must confirm that manufacturers carefully consider the routes/mechanisms of microbial contamination and product cross-contamination and effectively control both to provide suitable facilities and equipment for protein DS manufacture. This means, among other things, that heating, ventilation, and air conditioning (HVAC) systems should be appropriately designed and maintained; products and processes should be appropriately segregated; and equipment should be appropriately cleaned and sanitized. Although the manufacturer's microbial and product cross-contamination control strategies (including HVAC design and cleaning/sanitization validation) are typically evaluated before application approval, the inspection team must assess the firm's **maintenance** of microbial and cross-contamination control, including verification activities.

Many protein DS manufacturing processes support microbial proliferation because the media and the buffers used in production are conducive to microbial growth. Therefore, manufacturing processes should be designed with stringent controls to prevent adventitious microorganism introduction/ingress, limit microbial proliferation and persistence, and remove microorganisms from the process at certain points.<sup>18</sup> The inspection team should confirm that the manufacturer is maintaining adequate microbial controls over its processes. The inspection team should verify that in-process (i.e., bioburden and endotoxin) action limits established within the quality system are not exceeded and, if excursions occur, they are appropriately investigated and corrected. Additionally, the inspection team should confirm appropriate microbial control of raw materials,

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<sup>18</sup> Manufacturers may employ bioburden-reduction filtration to remove incidental bioburden from the process stream at critical points; however, the inspection team should verify that the firm is meeting **established prefiltration bioburden limits** (i.e., not using filtration steps to remove high levels of bioburden from process streams). This verification is important because filtration does not remove microbial byproducts such as bacterial endotoxin and proteolytic enzymes, the latter of which can decrease product potency, decrease product stability, and change product impurity profiles.

including water used for manufacturing (e.g., verify proper maintenance and control of water production systems).<sup>19</sup>

The inspection team should note:

- From a microbial control perspective, facility and equipment requirements for upstream processes generally do not need to be as stringent for microbial fermentation as they do for mammalian cell culture. Similarly, establishments using completely closed systems may have less stringent room air quality requirements than establishments that do not.
- Because cross-contamination prevention is complex, multifaceted, and dependent upon proper control of both equipment and facilities, it is addressed in its own section within this system (Part III.4.C—[Cross-Contamination Prevention](#)).
- Most protein DS establishments do not manufacture highly potent or toxic products and do not use spore-forming microorganisms for production. However, if the establishment being inspected does manufacture these products or use these microorganisms, specific and thorough coverage relevant to the Facilities and Equipment system is warranted. A narrative that guides the focus of these investigations, along with specific questions, can be found in the following attachments:
  - Attachment B—[Highly Potent or Toxic Products](#)
  - Attachment C—[Spore-Forming Microorganisms](#)

## A. Equipment

### (1) General

The inspection team should inspect equipment in the facility to evaluate its physical integrity, installation, working conditions, and maintenance. The inspection team should confirm that there is adequate documentation and management of deviation and failure investigations (e.g., performing appropriate CAPAs in a timely manner).

See Attachment A—[General](#)—for pertinent questions.

### (2) Equipment Qualification and Requalification

The inspection team must verify that the firm has qualified new equipment, focusing its coverage on critical equipment. Additionally, the inspection team should verify that the firm is appropriately monitoring the performance of already qualified equipment, ensuring that repurposed (e.g., old) equipment is appropriate and periodically evaluated to verify that the

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<sup>19</sup> This compliance program applies to manufacturing of protein DS that is intended for use in producing commercial sterile injectable biological products (the majority of biological products); however, a few biological products are administered orally (e.g., pancreatic enzyme products). For orally administered biological products, expectations for the protein DS microbial control may differ from expectations for parenteral products and, hence, may not be as stringent as those discussed in this compliance program.

equipment remains in a validated state and is suitable for its intended use. The inspection team must verify that equipment has been requalified, as appropriate, based on level of risk (e.g., the equipment has undergone major changes or repairs or has been implicated in a manufacturing deviation or failure). Requalification may not need to be as in-depth as initial qualification; however, if requalification is appropriate, activities should be sufficient to verify suitable performance.

Equipment qualification is also covered in the laboratory control system section (see Part III.7.A(4)—[Laboratory Equipment, Reagents, and Standards](#)) and the production system section under specific unit operations (see Part III.6).

References:

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

See Attachment A—[Equipment Qualification and Requalification](#)—for pertinent questions.

### **(3) Equipment Maintenance and Calibration**

The inspection team should verify that the firm maintains and calibrates equipment for the range of operation and, as necessary, that it can provide reasonable justification for practices that are less rigorous than equipment vendor recommendations. The inspection team should focus coverage on pieces of equipment implicated or potentially implicated in recent manufacturing deviations/failures.

Reference: ICH Q7, sections V.B, Equipment Maintenance and Cleaning, and V.C, Calibration

See Attachment A—[Equipment Maintenance and Calibration](#)—for pertinent questions.

### **(4) Equipment Cleaning**

Protein DS manufacturers should be using validated cleaning procedures for nondisposable equipment that contacts protein DS directly.

Generally, original cleaning validation should be completed before an application or manufacturing supplement is approved. Therefore, on surveillance inspections, the inspection team should focus on the execution of those validated cleaning procedures as well as the firm's continued verification activities.

References:

- ICH Q7, sections V.B, Equipment Maintenance and Cleaning, and XII.G, Cleaning Validation

- Guide to inspections *Validation of Cleaning Processes* (1993)<sup>20</sup>
- Parenteral Drug Association (PDA) Technical Report No. 49 *Points To Consider for Biotechnology Cleaning Validation* (2010)

See Attachment A—[Equipment Cleaning](#)—for pertinent questions.

### **(5) Equipment Sanitization and Sterilization**

In general, manufacturers should use sterile equipment for cell culture/fermentation processes, although in some situations, it may be acceptable to sanitize microbial fermenters. Equipment for purification processes may be sterilized or sanitized. The inspection team must conduct inspections on ongoing sanitization and sterilization, including verification and requalification at the frequency described in the quality system or as indicated by changes in the facility microorganisms or frequency of contamination events. Requalification should be considered following major equipment repairs or changes or the failure of sanitization/sterilization processes.

Reference: PDA Technical Report No. 1 *Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control* (2007) (This technical report is intended for the steam sterilization of small parts; however, many of the general concepts may be applied to large equipment or sterilize-in-place systems.)

See Attachment A—[Equipment Sanitization and Sterilization](#)—for pertinent questions.

### **(6) Disposable Equipment**

Disposable equipment should be integral and single-use only. The firm should diligently seek to resolve leakage issues by determining actual or potential root causes and implementing appropriate CAPAs. The firm should adequately evaluate the leakage's impact on affected product.

See Attachment A—[Disposable Equipment](#)—for pertinent questions.

### **(7) Computerized Systems**

CGMP-related computerized systems should be validated. The depth and scope of computerized system validation depends on the diversity, complexity, and criticality of the application. The firm should have suitable written procedures available for the operation and maintenance of computerized systems.

Reference: ICH Q7, section V.D, Computerized Systems

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<sup>20</sup> FDA's inspection guides are found at <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-guides>.

See Attachment A—[Computerized Systems](#)—for pertinent questions.

## B. Facilities

### (1) Water

Water systems can present significant challenges in a protein DS establishment because of the volume of water generated and used. If water systems are not properly maintained, problems can arise, such as microbial biofilm formation. Although water systems should have appropriate alert and action limits, WFI samples are expected to generally yield zero viable cell counts. Therefore, routine viable counts for WFI systems (even if below the alert limit) or endotoxin levels found at or above the specified limit may indicate there are issues that need to be investigated and CAPAs that should be introduced.

WFI is generally used in the production of protein DS, although purified water may be used in microbial fermentation processes and for initial equipment rinses when cleaning. For each water type used during manufacturing, the firm should set appropriate specifications based on the water type's intended use and should maintain appropriate records that demonstrate that the water type meets compendial standards and established specifications. Manufacturers should use higher quality water as the manufacturing process proceeds downstream. Firms should never employ water of lower quality than WFI in the late stages of the manufacturing process.

#### References:

- ICH Q7, section IV.C, Water
- Guide to inspections *High Purity Water System* (1993)
- International Society for Pharmaceutical Engineering (ISPE) Baseline Guide Volume 4 *Water and Steam Systems* (2011)
- Purified Water, USP (United States Pharmacopeia)
- Water for Injection, USP

See Attachment A—[Water](#)—for pertinent questions (including questions about water as a material).

### (2) Process Gases

Process gases generated on-site may include, but are not limited to, compressed air, oxygen, and nitrogen. These gases may be used in upstream and downstream manufacturing operations. Gas supply systems should be appropriately maintained, and manufacturers should be able to demonstrate—through qualification, periodic testing or monitoring, and requalification (as appropriate)—that these systems are consistently able to produce material that is suitable for its intended use.

Reference: ISPE Good Practice Guide *Process Gases* (2011)

See Attachment A—[Process Gases](#)—for pertinent questions (including questions about process gas as a material). If applicable, questions cover gases purchased by the firm.

### (3) Clean Steam

Because clean steam can encounter product-contact surfaces, the clean steam condensate quality specifications should not be inferior to compendial (USP) standards for WFI.

See Attachment A—[Clean Steam](#)—for pertinent questions.

### (4) HVAC Systems

HVAC systems are essential for providing suitable environments for protein DS production, especially for *open* operations performed when a component or protein DS is exposed to the immediate environment and therefore susceptible to contamination from the surrounding air. HVAC system design and the appropriate segregation of operations (generally evaluated during preapproval inspections (PAIs) or prelicense inspections (PLIs)) should be sufficient to control contamination and cross-contamination, including contamination from upstream production steps in the same manufacturing process. Of particular concern for **mammalian** cell culture is the susceptibility to adventitious agents (e.g., viruses, mycoplasma) and the potential to spread these agents throughout the manufacturing environment. Manufacturing processes involving mammalian cell lines typically include viral clearance/inactivation steps, and HVAC systems should function to maintain the segregation of pre- and post-viral clearance/inactivation steps.<sup>21</sup> HVAC systems are generally a point of focus during product-related PLIs and PAIs. Surveillance inspections should focus on the maintenance of HVAC systems and the demonstration that these systems continue to function as intended.

References:

- ICH Q7, section IV.B, Utilities
- ISPE Good Practice Guide *Heating, Ventilation, and Air Conditioning* (2009)

See Attachment A—[HVAC Systems](#)—for pertinent questions.

### (5) Facility Cleaning and Disinfecting

Facilities should be appropriately cleaned and disinfected to ensure sufficient microbial control. Firm should have established, validated cleaning and sanitizing procedures and be able to provide justification for established residual limits using validated analytical testing methods.

References:

- ICH Q7, section IV.G, Sanitation and Maintenance

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<sup>21</sup> In this document, areas up to viral clearance/inactivation are *pre-viral* areas and areas after viral clearance/inactivation are *post-viral* areas.

- USP General Chapter <1072> *Disinfectants and Antiseptics*

See Attachment A—[Facility Cleaning and Disinfecting](#)—for pertinent questions.

### **(6) Facility Environmental Monitoring**

The firm's environmental monitoring (EM) data should demonstrate HVAC system effectiveness as well as the adequacy of the facility's cleaning and sanitization programs. EM frequency and acceptance criteria should be suitable for each stage of production and the types of operations conducted in specific areas. The EM data should be adequate to support root cause investigations for contamination events.

Reference: PDA Technical Report No. 13 (Revised) *Fundamentals of an Environmental Monitoring Program* (2014) (Although the primary scope of this document is sterile drug product manufacturing, it provides useful information for any controlled environment.)

See Attachment A—[Facility Environmental Monitoring](#)—for pertinent questions.

### **(7) Pest Control**

Pest control is an important consideration in preventing contamination of raw materials, equipment, and protein DS.

See Attachment A—[Pest Control](#)—for pertinent questions.

### **C. Cross-Contamination Prevention**

Protein DS manufacturing processes should be designed and executed to prevent cross-contamination between different product processes; areas that do and do not use animal-derived components; pre- and post-viral activities; and upstream and downstream operations. Manufacturers should integrate facility and equipment CGMP concepts to effectively prevent product cross-contamination. These concepts include:

- Appropriate segregation or containment of different manufacturing processes or process steps.
- Appropriate flow of personnel, products, raw materials, waste materials, and equipment.
- Adequate procedural controls.
- Appropriate changeover activities.
- Adequate validation and verification for the cleaning of shared product-contact equipment (with inactivation procedures as necessary).
- Adequate personnel training.

When evaluating a firm's cross-contamination prevention measures, the inspection team must evaluate not only the details of the individual measures, but also how these measures fit together



to form a single, robust cross-contamination control system. Because of the inherent complexity of cross-contamination prevention, there are many opportunities for failure, which could pose significant patient safety risks.

When evaluating cross-contamination prevention, the inspection team should keep the following principles in mind:

- For campaign-based manufacturing activities (time-based segregation of different manufacturing processes in the same manufacturing area), appropriate changeover procedures between product manufacturing campaigns are critical for the prevention of product cross-contamination.
- For firms conducting different manufacturing activities simultaneously in physically separated areas, the awareness and control of potential crossover points and other opportunities for cross-contamination (e.g., in shared washing areas, personnel movement) are of key importance.
- Firms engaged in concurrent manufacturing (conducting multiple manufacturing processes in the same area) should be able to demonstrate there are sufficient controls to prevent cross-contamination.
- Firms manufacturing protein DS using equipment that is not product-dedicated (i.e., shared), regardless of how manufacturing activities are segregated or contained, should also ensure adequate cleaning of such equipment.
- Firms should ensure that personnel are adequately trained to prevent cross-contamination and that appropriate procedures are in place to direct the flow of personnel, products, raw materials, waste materials, and equipment.

See Attachment A—[Cross-Contamination Prevention](#)—for pertinent questions.

## 5. Materials System

The materials system covers the measures and activities that ensure the quality of materials used in protein DS manufacture and packaging, regardless of whether those materials are present in the final bulk DS. The general principles for auditing this system are consistent with those described in compliance program 7356.002; however, the inspection team should place emphasis on:

- **Changes in the source of a material.** The complex nature of protein DS manufacturing processes means that these processes may be more susceptible than most to the unintended consequences of change, including changes to raw materials, which can significantly affect final product characteristics. The firm should have an inventory of these materials that includes their source, use, and criticality ranking for their potential to introduce contaminants or alter the final product.
- **The establishment's ongoing approach to ensure material suitability.** The establishment should have an adequate program for monitoring and detecting changes in

raw material quality, regardless of whether suppliers have reported changes. Raw material variability can significantly impact drug quality.

- **Control of material microbial/adventitious agent characteristics, particularly for those materials of biological origin.** Manufacturers should ensure freedom from adventitious agents, including mycoplasma and viruses, in accordance with application requirements. For materials of **bovine** origin, the firm should ensure freedom from transmissible spongiform encephalopathy (TSE) agents. Microbial tests, including those for adventitious agents, are covered in the laboratory control system section (see Part III.7.C—[Microbiological Testing](#)).
- **Storage and handling of MCBs and WCBs.** Protein quality characteristics are strongly tied to the cells from which they are produced; therefore, the cell banks should be appropriately controlled and defined.

#### References:

- ICH guidance for industry *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin* (September 1998)
- ICH Q7, sections VII, Materials Management, and VI.C, Records of Raw Materials, Intermediates, API Labeling and Packaging Materials

#### A. Raw Materials

Critical raw materials are those that may impact the quality of protein DS and thus impact product safety and efficacy. The inspection team should confirm that the manufacturers have a robust PQS ensuring appropriate microbiological control of raw materials, including water.<sup>22</sup> The inspection team should also verify that the firm adequately monitors and documents all aspects related to critical raw material, including, for example, sourcing and vendor qualification, management of inventory, and testing and release of these materials.

See Attachment A for questions related to [Sourcing and Vendor Qualification](#); [Receipt, Inventory, and Storage of Materials](#); and [Testing, Examination, and Release of Materials](#).

#### B. Cell Banks

To ensure the uninterrupted production of protein DS of consistent quality, manufacturers should appropriately store, maintain, and handle MCBs and WCBs.<sup>23</sup> Firms should restrict cell bank

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<sup>22</sup> This compliance program was developed to cover protein DS intended for manufacturing sterile injectable drug product (i.e., the majority of protein products); however, if a protein product will be administered orally or topically, the expectations for microbial control may differ significantly from expectations for injectable products and, hence, may not be as stringent as those discussed in this compliance program.

<sup>23</sup> If product cell lines are to be used over many manufacturing cycles, a two-tiered cell banking system consisting of an MCB and a WCB is generally employed and usually described in the relevant BLA. However, some products

access, appropriately segregate different cell lines, store cells at appropriate temperatures, monitor the storage areas for temperature excursions, and account for aliquot removal. Liquid nitrogen freezers using liquid/vapor phase storage are often used. Because the catastrophic failure of a cell bank could halt production of a sole-source or medically necessary product, manufacturers should store cell banks in multiple distinct locations, preferably at separate facilities. Cell banks should be tested for identity, purity, and stability as described in ICH guidance for industry *Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* (September 1998).

The creation, qualification, and use of new commercial WCBs postapproval can be reported in a supplement to the application and are often performed under an FDA-approved protocol. If an FDA-approved protocol is used, a lower reporting category for the creation, qualification, and implementation of a new WCB may have been agreed to by FDA (e.g., changes being effected (CBE) or annual report).

The inspection team must **immediately** notify CDER of any unreported changes in the cell banks affecting commercial product.

References:

- ICH Q5A
- ICH guidance for industry *Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products* (February 1996)

See Attachment A—[Cell Banks](#)—for pertinent questions.

## 6. Production System

A firm's production system includes production processes, in-process sampling, and in-process controls. From a risk perspective, the inspection team should attend to the following when covering a protein DS manufacturer's production system:

- Process consistency.
- Clearance of impurities, including high-risk process- and product-related impurities.
- Meeting in-process limits, including in-process bioburden and endotoxin action limits, and release specifications.

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manufactured using microbial expression systems may not have a two-tiered system—a transformation may be performed for each new cell substrate container lot. The transformed cell substrate lot is considered the MCB and is the source material for production runs.

- Stringent controls to prevent adventitious microorganism contamination throughout the production process.<sup>24</sup>
- Viral clearance/inactivation (if applicable).
- Process changes.

Steps common to the production of protein DS are discussed briefly in Part I.4—[General Overview of Protein DS Manufacturing Processes](#) and, where appropriate, in the sections below.

The inspection team should verify that protein DS are manufactured in strict conformance with approved, validated processes to ensure the desired clinical outcome. Process- and product-specific manufacturing details can be found in relevant BLAs. The inspection team should reference these applications throughout the inspection. However, the inspection team should not assume that aspects of the control strategy defined as *critical* by the firm, including those defined as critical in the application, are the only aspects required to ensure the safety and efficacy of the protein DS. For example, all process parameters and in-process controls included as established conditions in the BLA ensure product safety and efficacy. Similarly, all attributes included in the control strategy may be important, regardless of whether the firm or applicant has listed them as critical quality attributes. Use of the term *critical* throughout this compliance program may not align with the firm's use of the term. The inspection team should contact CDER product specialists identified in the site dossier when assistance is needed to determine criticality, if appropriate.

When inspecting production processes, the inspection team should note that high-risk impurities differ from process to process and depend on things such as the products themselves as well as the expression systems and raw materials employed. Potentially relevant high-risk impurities include, but are not limited to, host cell proteins, host cell DNA, residual antifoam and antishear materials, metals and other ligands from affinity chromatography columns, cyanide from PEGylation processes, and product-related impurities (e.g., protein aggregates, high and low molecular weight moieties).

Reference: ICH Q7, section VIII, Production and In-Process Controls

#### A. General

Section A under Production System is not associated with specific unit operations. As appropriate, the inspection team should apply the section A questions linked to below to the unit operations covered under Production System in sections B through J.

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<sup>24</sup> Manufacturers may employ bioburden-reduction filtration to remove bioburden from the process stream at critical points; however, the inspection team should verify that the firm is meeting **established prefiltration bioburden limits** (i.e., not using filtration steps to remove high levels of bioburden from process streams). This verification is important because filtration does not remove microbial byproducts such as bacterial endotoxin and proteolytic enzymes, the latter of which can decrease product potency, decrease product stability, and change product impurity profiles.

### (1) Personnel

Production personnel should be qualified, trained, and attentive to hygiene.

Reference: ICH Q7, sections III.A, Personnel Qualifications, and III.B, Personnel Hygiene

See Attachment A—[Personnel](#)—for pertinent questions.

### (2) Master and Batch Production Records

Firms should have appropriately controlled master and batch production records that accurately reflect their manufacturing processes. When auditing a firm's records (production, laboratory, or otherwise), the inspection team should focus on record/data integrity. Although FDA inspection teams have occasionally observed intentional record falsification, data integrity issues stemming from poor documentation practices are significantly more prevalent (e.g., operations are not recorded contemporaneously, records are not complete and accurate). Therefore, the inspection team should review documentation practices to determine whether they are appropriate (see also Part III.3.O—[Data Integrity](#)).

Reference: ICH Q7, sections VI.D, Master Production Instructions, and VI.E, Batch Production Records

See Attachment A—[Master and Batch Production Records](#)—for pertinent questions.

### (3) In-Process Sampling and Controls

As discussed in ICH Q7, manufacturers should establish procedures that “monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs,” with related sampling plans and procedures “based on scientifically sound sampling practices.”

Reference: ICH Q7, section VIII.C, In-Process Sampling and Controls

See Attachment A—[In-Process Sampling and Controls](#)—for pertinent questions.

### (4) Excursions, Deviations, and Failures

The inspection team should review an appropriate number of records documenting investigation excursions, deviations, and failures across multiple systems using questions linked to below.

See Attachment A—[Excursions, Deviations, and Failures](#)—for pertinent questions.

### (5) Process Validation

**Prospective** validation, which is typically covered during PLIs or PAIs, may include, but is not limited to, studies for individual unit operations, in-process hold times, buffer and media hold times, viral clearance, impurity clearance, column resin lifetime (at reduced scale), and shipping.

**Concurrent** validation studies include studies for UF/DF membrane lifetimes, column resin lifetimes (at manufacturing scale), and reprocessing steps. The firm’s approach to process validation should be consistent with a lifecycle approach to validation, as discussed in guidance for industry *Process Validation: General Principles and Practices*.

See Attachment A—[Process Validation](#)—for pertinent questions.

## (6) Reworking and Reprocessing

ICH Q7 defines *reworking* as “Subjecting an intermediate or API that does 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.” The inspection team should **immediately** email [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc: [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov), providing details for operations that would fit ICH Q7’s definition of reworking, if the firm cannot provide evidence that the rework in question has been covered by an appropriate FDA submission.

ICH Q7 defines *reprocessing* as “introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps ... that are part of the established manufacturing process.” Because of the greater potential for unintended impacts on product quality, the inspection team should encounter protein DS reprocessing much less frequently than small molecule API reprocessing. The inspection team should **rarely** encounter protein DS reprocessing steps that have not either been specifically approved in the relevant BLA or appropriately reported to FDA. An example of reprocessing that might be specifically covered by a BLA would be repeating viral filtration following a failed filter integrity test. Because viral filters occasionally fail, manufactures may be approved for refiltration of the protein DS (following successful validation).

Occasionally, an applicant will submit a prior approval supplement to FDA to cover reprocessing of a specific batch, perhaps in response to a manufacturing deviation. The inspection team should critically evaluate any reprocessing that may indicate that the process is not operating within a state of control, regardless of whether the applicant has submitted such a supplement.

If the firm intends to distribute (or has distributed) material reprocessed in a manner not reported to FDA or specifically covered by the BLA, the inspection team should email the details of the reprocessing steps to [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc: [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov). The email will be forwarded to the appropriate CDER product specialist for response. Reprocessing steps should generally be accompanied by validation. In some cases, concurrent validation may be considered acceptable.

See Attachment A—[Reworking and Reprocessing](#)—for pertinent questions.

## B. Weighing and Dispensing of Materials

Material weighing and dispensing should be controlled. Operations should be performed with sufficient accuracy and in a manner that does not affect the material's suitability for use or cause cross-contamination.

Reference: ICH Q7, section VIII.A, Production Operations

See Attachment A—[Weighing and Dispensing of Materials](#)—for pertinent questions.

## C. Media and Buffer Preparation and Holding

Media and buffers should have adequate control procedures.

See Attachment A—[Media and Buffer Preparation and Holding](#)—for pertinent questions.

## D. Cell Culture and Production-Scale Expression

Protein DS manufacturing processes generally begin with the thawing of a WCB vial, the contents of which are used to start one or more seed trains, which are, in turn, used to start one or more inoculum trains. The inoculum trains are then used to begin growth/expression in production scale fermenters/bioreactors. Throughout the expansion process, as the cell culture volume increases, several types of cell culture vessels may be used, each of which have their own process controls. Vessels include shaker flasks, spinner flasks, roller bottles, cubes, and wave bags as well as small-scale fermenters/bioreactors. The most commonly used reactor is a stirred-tank reactor, but others, such as air lift bioreactors, hollow fiber bioreactors, and ceramic cartridge bioreactors, may be used. Additionally, roller bottles and disposable bioreactors may be employed. Cells may grow in suspension (most common), on microcarriers, or, on rare occasions, a fixed solid phase. Production-scale growth/expression may occur, for example, when using:

- A single-batch closed system.
- A fed-batch system (nutrients added periodically).
- Perfusion: Cells are held at high density while waste and the desired protein are continuously removed and nutrients are continually added.

Systems that are not closed should maintain microbial control, with the level of control commensurate with the level of risk. Very long production operations, such as those involving perfusion, are considered high-risk from a microbial contamination perspective.

BLAs should serve as reference for cell culture and expression process controls and process parameters.

Manufacturers should test the unprocessed bulk for viruses, mycoplasma, and bioburden, as applicable (and in conformance with application commitments). (See also the laboratory control system at Part III.7.C(4)—[Viral Safety Testing](#).)

See Attachment A—[Cell Culture and Production-Scale Expression](#)—for pertinent questions.

#### E. Post-Expression Harvest and Recovery

Following production-scale expression, the contents of the fermenter/bioreactor (known as unprocessed, unclarified, or unpurified bulk) will be subjected to one or more harvest or clarification steps to separate cellular matter from the cell culture medium/supernatant and produce the clarified bulk. Steps may include centrifugation (generally continuous), depth filtration, standard membrane filtration, or tangential flow filtration. Harvest and clarification controls may include centrifuge type, centrifuge flow rate, centrifuge bowl speed, centrifuge temperature, filter type, depth filtration differential pressure, filtration temperature, filtration flux, filter re-use cycles, harvest vessel temperature and hold time, harvest bioburden, and harvest endotoxin. Harvest and clarification parameters should always be consistent with application commitments.

Generally, the supernatant of the fermentation of nonmicrobial (e.g., mammalian) and yeast expression systems will contain the excreted protein DS, whereas for bacterial expression, the cellular/pelleted matter will contain the desired protein (although there are exceptions). If the cellular matter contains the protein DS, recovery of the desired protein requires cell disruption (e.g., treatment with lytic enzymes or physical disruption) followed by clarification. For proteins that have been expressed in the form of insoluble inclusion bodies (generally larger proteins expressed in microbial systems), the protein may require denaturation, followed by controlled refolding, chemical reduction, and concentration, to produce an active form of the protein.

See Attachment A—[Post-Expression Harvest and Recovery](#)—for pertinent questions.

#### F. Ultrafiltration/Diafiltration

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

Reference: PDA Technical Report No. 15 *Validation of Tangential Flow Filtration in Biopharmaceutical Applications* (2009)

See Attachment A—[Ultrafiltration/Diafiltration](#)—for pertinent questions.

#### G. Column Chromatography

Chromatography resins (e.g., affinity, cation/anion exchange, hydrophobic, size-exclusion) are generally re-used but should be product-dedicated. Chromatography column housings (hardware) need not be product-dedicated; however, the firm should have adequate cleaning validation and changeover procedures for nondedicated column housings. Resin 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 should be verified at scale.

If the firm uses specialty capture/affinity resins, such as Protein A, these should be a point of focus when covering purification. Specialty capture resins are often susceptible to degradation/ligand leakage. Therefore, the inspection team should verify that resins currently in use are within their validated cycle lifetimes and that recent operations have not demonstrated signs of resin deterioration. The inspection team should also cover the firm's activities to control or monitor the leakage of ligand into the product stream, such as material/vendor qualification and testing and, if applicable, routine monitoring or testing. Additionally, because the sanitization and storage conditions for resins that are susceptible to degradation may not be as harsh as those used for other resins, the inspection team should confirm adequate ongoing microbial control of these resins.

Reference: PDA Technical Report No. 14 *Validation of Column-Based Chromatography Processes for the Purification of Proteins* (2008)

See Attachment A—[Column Chromatography](#)—for pertinent questions.

#### H. Viral Clearance/Inactivation

All products manufactured in mammalian expression systems should have processes dedicated to viral clearance or inactivation. Recently approved products will almost always contain viral filtration steps in their manufacturing processes because of the proven effectiveness of this method. Common viral inactivation treatment methods include low pH, heat, detergent, and solvent. To ensure product safety, **viral clearance/inactivation processes should always be conducted in strict accordance with procedures approved by the quality unit and any changes managed through a robust PQS.**

References:

- ICH Q5A
- PDA Technical Report No. 41 *Virus Filtration* (2008)

See Attachment A—[Viral Clearance/Inactivation](#)—for pertinent questions.

#### I. Bulk Drug Filtration and Fill

Most protein DS are not sterile. However, they are filtered to reduce bioburden. 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 a PAI or PLI. Factors affecting microbial control include use of open or closed systems, the growth promoting potential of the bulk, the microbial control risks during the drug product manufacturing process, and the storage temperature of the protein DS. Protein DS not stored frozen have the highest risk; therefore, open filling operations for these DS should be conducted under conditions designed to maintain

microbial control (e.g., safety cabinet or ISO 5 type of environment). Protein DS intended to be stored frozen should be frozen according to the approved application.

See Attachment A—[Bulk Drug Filtration and Fill](#)—for pertinent questions.

#### J. Bulk Storage of Protein DS

Typically, protein DS are frozen ( $\leq -15^{\circ}\text{C}$ ) during storage. However, there may be cases where some bulk protein DS may not be stable when frozen and are held at  $2-8^{\circ}\text{C}$ , requiring additional consideration when looking at microbial control.

For any approved storage temperature, the protein DS should be:

- Stored in the appropriate containers as indicated in the application.
- Protected from light if indicated in the application.
- Stored in a controlled and monitored freezer or other cooling device at a temperature as indicated in the application.
- Adequately labeled to prevent mix-ups.
- Stored in an area with controlled access and under appropriate conditions so that quality, purity, and strength are not affected.

See Attachment A—[Bulk Storage of Protein DS](#)—for pertinent questions.

### 7. Laboratory Control System

Laboratories overseeing the quality assurance and control of protein DS and their in-process intermediates comprise several analytical disciplines, including chemistry, biology, and microbiology. The firm should have appropriate procedures in place to routinely track method performance parameters and effectively manage signals/patterns of potential concern to prevent drift in assay performance away from validated operating conditions throughout the method's lifecycle. The inspection team will encounter familiar testing platforms, such as high performance liquid chromatography, as well as protein-specific testing platforms, such as polyacrylamide gel electrophoresis, isoelectric focusing, and cell-based assays, commonly called *bioassays*, designed to determine the potency of the protein DS. For background information on the characterization of protein DS, the inspection team should refer to ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999). The inspection team should contact CDER product specialists by emailing [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc'ing [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov) with questions regarding chemical or biological testing, such as test method performance or the acceptability of results. Because of the nature of protein DS manufacturing and the considerations discussed earlier in this compliance program, the inspection team should expect to see extensive microbiological testing. For microbiological method support, the inspection team should contact either ORA microbiology experts through ORA support networks or CDER

microbiology experts via [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov), cc'ing [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov).

Because of the need for specialized experience and equipment, it is common for some testing, such as potency testing, mycoplasma testing, and viral safety testing, to be conducted at establishments other than the protein DS manufacturer. Animal testing is rarely required, but when it is, it would likely not be conducted at the protein DS establishment.

Product in-process and release testing should be defined in relevant BLAs, which the inspection team should reference.

#### A. All Laboratory Disciplines

In general, the inspection team should approach protein DS testing operations as they would other CGMP testing operations. Many of the same expectations and principles apply, regardless of the specific test methods.

Specifications are not intended to fully characterize a drug substance (e.g., complete characterization of a protein's post-translational modifications), and meeting them does not guarantee quality. As discussed in ICH Q6B, "specifications are **one part** [emphasis added] of a total control strategy designed to ensure product quality and consistency."

References:

- ICH Q7, section XI, Laboratory Controls
- Guide to inspections *Pharmaceutical Quality Control Labs* (1993)

See Attachment A—[All Laboratory Disciplines](#)—for pertinent questions.

#### (1) Sampling

The inspection team should evaluate how the firm conducts sampling based on approved procedures using questions linked to below.

See Attachment A—[Sampling](#)—for pertinent questions.

#### (2) Test Methods

The inspection team should evaluate the firm's procedures to establish test methods using questions linked to below.

See Attachment A—[Test Methods](#)—for pertinent questions.

### (3) Record Keeping

The inspection team should cover record keeping using questions linked below but should also refer to Part III.3.O—[Data Integrity](#)—when covering laboratory record keeping because the questions linked in that section are applicable to all CGMP record keeping activities.

Reference: ICH Q7, section VI.F, Laboratory Control Records

See Attachment A—[Record Keeping](#)—for pertinent questions.

### (4) Laboratory Equipment, Reagents, and Standards

The inspection team should evaluate a sample of laboratory equipment, reagents, and chemicals to assess the firm's qualification, maintenance, and storage procedures.

See Attachment A—[Laboratory Equipment, Reagents, and Standards](#)—for pertinent questions.

### (5) Test Method Validation and Postapproval Changes

The inspection team should ensure that test methods have been validated and that postapproval changes are made in accordance with procedures approved by the quality unit and are reported appropriately.

References:

- ICH guidance for industry *Q2A(R1) Text on Validation of Analytical Procedures* (March 1995)
- ICH guidance for industry *Q2B(R1) Validation of Analytical Procedures: Methodology* (May 1997)
- ICH Q7, section XII.H, Validation of Analytical Methods
- ICH Q12
- Guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015)
- Draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products*<sup>25</sup>
- PDA Technical Report No. 57 *Analytical Method Validation and Transfer for Biotechnology Products* (2012)

See Attachment A—[Test Method Validation and Postapproval Changes](#)—for pertinent questions.

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<sup>25</sup> When final, this guidance will represent FDA's current thinking on this topic.

## (6) Out-of-Specification Results and Invalid Tests

The inspection team should review recent OOS test records. Invalid tests should not be part of the OOS records. A test should be considered invalid if, for example, the system suitability assessment has failed multiple times, highlighting potential issues with test method robustness.

For OOS investigations, retesting may be allowed under strictly defined conditions; however, procedures should be in place to determine whether retesting is appropriate, how retesting should be performed (e.g., sampling, duplicates), and how results should be interpreted.

Reference: Guidance for industry *Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production*<sup>26</sup>

See Attachment A—[Out-of-Specification Results and Invalid Tests](#)—for pertinent questions.

## (7) Stability Testing and Reserve Samples

The inspection team should evaluate the adequacy of the containers used to evaluate stability of the protein DS as well as the firm's record keeping practice related to stability testing results and triage and management of pertinent deviations and failures.

References:

- 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, sections XI.E, Stability Monitoring of APIs, and XI.G, Reserve/Retention Samples

See Attachment A—[Stability Testing and Reserve Samples](#)—for pertinent questions.

### B. Biotechnology-Specific Testing

#### (1) Potency Assays/Bioassays

Biological products are required to be tested for potency, with tests consisting “of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in § 600.3(s)” (21 CFR 610.10). Potency assays should be conducted for product release and stability testing as well as for comparability testing (comparing material from different manufacturing processes) following a manufacturing change.

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<sup>26</sup> This guidance does not apply to microbiological or biological assay OOS results.

Potency assessments can take many different analytical forms; however, they all examine a product's biological function. Potency assays may involve measurements of enzymatic activity or protein binding or they may be more complicated. For example, some potency assays are cell-based (commonly called bioassays) and are designed to measure activities such as cellular activation, cellular uptake, or cellular viral protection. Regardless of assay type, potency assays should have controls typical of analytical methods, such as system suitability.

For more information on biological activity assays, the inspection team should reference sections II.A.2 (Biological Activity) and II.A.3 (Immunochemical Properties) of ICH Q6B.

See Attachment A—[Potency Assays/Bioassays](#)—for pertinent questions.

## (2) Protein Reference Standards

Protein reference standards are generally prepared in-house by the firm or supplied by the applicant of the product to be tested. To ensure the suitability of these standards, manufacturers should create them according to defined procedures and sufficiently characterize them. Reference standard changes should be conducted per an approved protocol (as described in the relevant BLA) and are typically reported in an annual report. In the absence of an approved protocol, they should be handled through the submission of a supplement. In ensuring the suitability of reference standards for protein DS, the inspection team should confirm that reference materials have been or are being qualified or requalified by procedures used for routine DS release as well as additional characterization assays. The firm should also strictly follow storage conditions, usage conditions, and handling instructions for reference standards to avoid adding impurities and to ensure accurate analysis. Primary and secondary reference standards and materials are defined and discussed in the following ICH guidances for industry:

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

See Attachment A—[Protein Reference Standards](#)—for pertinent questions.

## C. Microbiological Testing

Protein DS manufacturing processes are particularly conducive to the growth of microorganisms, and because the resulting products are generally administered parenterally, it is essential for manufacturers to have adequate microbial testing and controls. Microbiological testing and controls, which CDER reviews before BLA approval, generally include:

- Screening raw materials for adventitious agents (see Part III.5—[Materials System](#)).
- Testing cell cultures before harvest for bioburden, mycoplasma, and other adventitious agents (e.g., viruses).
- Testing buffers and in-process materials for bioburden and endotoxin and observing established limits.

- Testing bulk protein DS for bioburden and endotoxin and observing established specifications.

BLAs themselves may serve as reference regarding the acceptability of a firm's microbiological testing practices. If the inspection team has questions or concerns regarding the suitability of a firm's microbiological and adventitious agent testing, they should contact CDER reviewers using contact information provided in the site dossier or by emailing [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc'ing [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov), where emails will be appropriately triaged to microbiologists.

References:

- Guide to inspections *Microbiological Pharmaceutical Quality Control Labs* (1993)
- USP General Chapter <1117> *Microbiological Best Laboratory Practices*

### **(1) Bacterial Endotoxin Testing**

The methods and conditions employed for bacterial endotoxin testing are approved with the approval of the BLA. Therefore, the inspection team should verify that the firm's validated bacterial endotoxin test is conducted as approved in the BLA and under the manufacturer's quality management system. The failure of an in-process material, raw material, or protein DS to comply with endotoxin action limits or specifications requires a thorough investigation into the root cause of the problem.

References:

- Guidance for industry *Pyrogen and Endotoxins Testing: Questions and Answers* (June 2012)<sup>27</sup>
- ANSI/AAMI ST72:2011(R2016), *Bacterial Endotoxins—Test Methods, Routine Monitoring, and Alternatives to Batch Testing*<sup>28</sup>
- USP General Chapter <85> *Bacterial Endotoxins Test*

See Attachment A—[Bacterial Endotoxin Testing](#)—for pertinent questions.

### **(2) Bioburden and Mycoplasma Testing**

Using validated and approved test methods, manufacturers should perform bioburden (microbial limits) testing on raw materials (as appropriate), in-process materials, and the protein DS. They should have and follow written procedures describing bioburden sample collection and the bioburden test method itself.

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<sup>27</sup> This guidance may be particularly useful to the inspection team covering bacterial endotoxin testing because it addresses 13 endotoxin testing questions, provides important information regarding critical product mixing before sample aliquot removal, and discusses the necessity of measuring pH values of the product-lysate mixture.

<sup>28</sup> ANSI=American National Standards Institute; AAMI=Association for the Advancement of Medical Instrumentation.

USP General Chapter <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* describes three specific methods to determine the microbial population of an in-process sample or protein DS. Although General Chapter <61> is often employed, some manufacturers may use other methods. The Attachment A questions linked to below are pertinent regardless of the microbial limits test method employed.

Cell banks and unprocessed bulk should be specifically tested for mycoplasma<sup>29</sup> if appropriate. Mycoplasma testing is expected for mammalian cell cultures. The expected mycoplasma control strategy for each protein DS should be detailed in the relevant BLA and may include the use of established compendial test methods. Because some raw materials may be a source of mycoplasma, manufacturers should test incoming raw materials as appropriate or have other controls in place (e.g., high temperature short time (HTST) processing or the use of 0.1 micron cell culture media filtration).

References:

- ICH guidance for industry *Q4B Annex 4A(R1) Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests General Chapter* (September 2010)
- PDA Technical Report No. 50 *Alternative Methods for Mycoplasma Testing* (2010)
- USP General Chapter <63> *Mycoplasma Tests*

See Attachment A—[Bioburden and Mycoplasma Testing](#)—for pertinent questions.

### (3) Identification of Microorganisms

Identification of microorganisms recovered from the product and the manufacturing environment can provide important information for investigations into the origin and source of non-host cell contaminants in protein DS manufacturing operations, thereby aiding the prompt resolution of microbial issues. Accurate identification of contaminants and their source (e.g., equipment cleaning, sanitization process) may be important in reaching conclusions concerning potential product impact.

References:

- Guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, section X.B, Microbiological Media and Identification (September 2004)
- USP General Chapter <1113> *Microbial Characterization, Identification, and Strain Typing*

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<sup>29</sup> Mycoplasma are a family of bacterium that lack cell walls, are largely unaffected by common antibiotic agents, and often possess the ability to pass through sterilizing grade filters. However, most are readily recovered using mycoplasma-specific growth media.



See Attachment A—[Identification of Microorganisms](#)—for pertinent questions.

#### (4) Viral Safety Testing

FDA expects manufacturers of protein DS to conduct viral safety testing if appropriate. Because of the potentially serious health consequences of viral contamination of an injectable product, testing for viruses at various process points is critical for protein DS derived from cell lines of human or animal origin.

The primary guidance for viral safety testing of biotechnological products is ICH Q5A. Per ICH Q5A, viral safety should be ensured through raw material controls, appropriate viral clearance after cell culture and during purification, the testing of cell banks (including end-of-production cell banks), and the testing of unprocessed bulk. The viral safety testing required for protein DS should be as described in BLAs.

Animal-derived raw materials are often tested based on their source (e.g., calf serum is tested for bovine viruses). Tests are often performed by raw material vendors; however, protein DS manufacturers should not rely on certificate of analysis (COA) testing results unless they have appropriately qualified the vendors, with appropriate activities to ensure *continued* vendor qualification, based on a risk assessment. (See also Part III.5—[Materials System](#).)

See Attachment A—[Viral Safety Testing](#)—for pertinent questions.

#### D. Contract Testing Laboratories

The use of contract laboratories is particularly common for, but not necessarily limited to, adventitious agents testing and required animal testing. If the protein DS manufacturer has assumed responsibility for contracting off-site testing operations (by virtue of being the product owner or having reached an agreement with the product owner to arrange for such testing), the firm's quality management system should ensure that the off-site tester is appropriately qualified to perform the testing. This means establishing confidence in the contract laboratory's test results and reviewing and confirming those results, as necessary. In addition, the protein DS manufacturer should have a quality agreement with the contract testing establishment detailing responsibilities such as reporting deviations, reviewing and reporting OOS results, and reviewing raw data. The inspection team should assess written quality agreements between the manufacturer and contracted laboratories, specifically focusing on the manufacturer's responsibilities for reviewing OOS results, setting product specifications, and selecting test methods.

Reference: Guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements*

See Attachment A—[Contract Testing Laboratories](#)—for pertinent questions.

## 8. Packaging and Labeling System

To provide assurance of drug quality, manufacturers should appropriately package, label, and ship the protein DS they manufacture.

Manufacturers should use the containers described in relevant BLAs, and the containers should be closed as described in the applications (e.g., to a specified torque for screw cap containers). Bulk containers of protein DS should be free of leaks. If a manufacturer experiences leakage, the event should be investigated, the potential product impact should be evaluated, and the manufacturer should be able to provide sound, scientific reasoning for the related disposition decision. Additionally, because of the potential for theft and counterfeiting, manufacturers should ensure that containers have been appropriately secured (e.g., using anti-tampering devices).

Manufacturers should confirm that printed labels contain the correct information and conform to specifications in the master production record. They should destroy excess, obsolete, and outdated labels and should have procedures to reconcile discrepancies between the numbers of labels issued and used, investigating discrepancies if appropriate. Because a single batch of bulk protein DS is often filled into multiple containers, the inspection team should confirm that manufacturers consistently label these containers with the appropriate batch number. To avoid potential mix-ups, manufacturers should also segregate batches of bulk protein DS from one another by physical or other suitable means.

Finally, manufacturers should ship their protein DS in accordance with validated shipping procedures, using qualified shippers.

Reference: ICH Q7, section IX, Packaging and Identification Labelling of APIs and Intermediates

See Attachment A—[Packaging and Labeling System](#)—for pertinent questions.

## 9. Sampling

CDER rarely requests sample collections and will provide specific instructions with any requests made.

If CDER does not request a sample collection, but the inspection team believes one is warranted, the inspection team should contact OQS by emailing [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc'ing [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov) for guidance before the sample collection. Samples may be collected to document suspected contamination or adulteration of raw materials, in-process materials, and protein DS encountered during an inspection; however, physical sample analysis is not necessary to document CGMP deficiencies.

If physical sample collection is warranted, CDER will provide specific instructions to ensure evidentiary sample controls are maintained. Sampling may be performed by the firm's personnel under FDA observation or performed by FDA staff with experience collecting evidentiary samples.

All samples should be collected as directed in a sample collection memo or in accordance with chapter 4 of the *Investigations Operations Manual* and section 702 of the FD&C Act.

## PART IV—ANALYTICAL

Routine sample collection under this compliance program is not anticipated.

As discussed in Part III.9—[Sampling](#), the inspection team should contact CDER before any samples are collected, with the exception of samples collected to document interstate commerce.

## PART V—REGULATORY/ADMINISTRATIVE STRATEGY

Inspection findings that demonstrate that a firm is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative, and/or judicial actions.

### 1. Reporting

The initial inspection classification should be based on the ORA division's assessment of the seriousness of the CGMP deficiencies. As appropriate, CDER product specialists should be consulted to evaluate the potential for product impact. Product specialists should provide feedback to the ORA division in a timely manner.

An inspection report that documents that one or more manufacturing systems is out of control should receive an initial Official Action Indicated (OAI) classification. The endorsement of the inspection report should describe the firm's actions that have been taken or will be taken and the planned time frame. All deficiencies should be addressed by stating the firm's corrective actions, accomplished or projected, for each deficiency as established in the discussion with management at the close of the inspection. All corrective actions proposed by firms are monitored and managed collaboratively by the ORA division and the Office of Manufacturing Quality (OMQ) in CDER's Office of Compliance.

FDA laboratory tests that demonstrate effects of absent or inadequate CGMP are strong evidence for supporting regulatory actions. Such evidence development should be considered as an inspection progresses and deficiencies are found. However, the lack of violative physical samples is not a barrier to pursuing regulatory and/or administrative action provided that CGMP deficiencies have been well documented. Likewise, physical samples found to be in compliance are not a barrier to pursuing action under CGMP charges.

The inspection findings will be the basis for updating profile classes in FACTS. Issuing a warning letter or taking other regulatory or advisory actions pursuant to a surveillance inspection should result in the classification of all profile classes as unacceptable.

### 2. General Considerations for FDA's Regulatory Action Strategies

Consistent with FDA practices discussed in the *Regulatory Procedures Manual*, FDA considers the following when determining its regulatory action strategy for noncompliant protein DS manufacturers:

- Regulatory significance of the inspectional observations, based on potential product quality impact and subsequent patient risk.
- Other information pertaining to the deficiencies, such as whether they were flagrant or intentional or whether the firm was aware and failed to correct.
- Acceptability of the firm's 483 response.
- The firm's compliance history.

- FDA’s judgment as to whether the firm is likely to comply voluntarily.

To provide examples of inspectional observations with differing regulatory significance, CDER and ORA biological product and CGMP subject matter experts categorized examples of significant CGMP deficiencies by their severity—critical or noteworthy; these examples are found on the next few pages of this compliance program. For the purposes of this compliance program:

- **Critical deficiencies** are deficiencies whose severity greatly exceeds the minimum threshold for regulatory significance.
- **Noteworthy deficiencies** are deficiencies that meet the threshold for regulatory significance.<sup>30</sup> Although not as significant as critical deficiencies, these may nevertheless lead to enforcement action if not promptly and adequately corrected.

Deficiencies were categorized by assessing the potential of each to impact product safety and efficacy (i.e., the potential for patient risk).<sup>31</sup> This categorization:

- Specifically guides the regulatory decision-making process if these deficiencies are observed. (See Part V.4.)
- Provides a baseline for determining the severity of deficiencies that are not specifically included in the examples below.

When determining the severity of a deficiency not specifically included below, COs should assess the deficiency’s potential safety and efficacy impacts, seeking input from CDER product specialists, manufacturing experts, and clinical experts, as appropriate. Severity need not be based solely on **known** risks. If FDA experts believe that a deficiency introduces a high level of uncertainty regarding the quality of a product in general, that deficiency should be categorized as noteworthy (and potentially, critical).

#### Critical Deficiencies: Examples

- Release of DS that does not conform to final specifications or is clearly of unacceptable quality.
- Failure to conduct an investigation (including an OOS testing result investigation) when evidence suggests that the safety, purity, or potency of a released DS has been adversely impacted.
- Multiple instances of inadequate OOS investigations, followed by material acceptance.

<sup>30</sup> A noteworthy deficiency could stem from implementation failures related to a change that PIC/S classifies as a major risk to the affected system; see PIC/S, *How To Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management*.

<sup>31</sup> In some cases, the severity of an observation could change (decrease or increase) on the basis of mitigating or aggravating circumstances. Seek FDA expert input if recategorizing the severity of observations.

- Failure to adequately investigate serious and unexpected adverse events that may be related to the DS.
- Failure to take appropriate actions when a DS fails stability testing under recommended storage conditions.
- Failure to properly maintain a facility or equipment to the extent that filth or insanitary conditions are apparent.
- Failure to properly maintain critical pieces of equipment such as fermenters/bioreactors, centrifuges, chromatography columns, and UF/DF equipment to the extent that the state of disrepair led to batch failures or product recalls.
- Gross failure to prevent product cross-contamination, especially from highly potent or toxic compounds (e.g., the inappropriate cleaning of shared product-contact equipment during changeover).
- Failure to evaluate the change of a critical raw material (e.g., an animal-derived raw material) and appropriately report the change to FDA.
- Unjustified use of a critical raw material that does not meet specifications.
- Failure to ensure that materials are free from adventitious agents as required.
- Failure to store cell banks under conditions that maintain the initial characteristics of the organisms and prevent mix-ups, contamination, and deterioration.
- Release of DS that was produced using a WCB that was neither approved in the application nor created and qualified in accordance with an FDA-approved protocol.
- Release of DS associated with an MCB that was not reported to FDA.
- Release of DS using a protein reference standard that was neither approved in the BLA nor qualified using an FDA-approved protocol.
- Release of DS that was manufactured in a manner clearly inconsistent with the BLA.
- Release of DS produced under conditions where viral inactivation or clearance operations were not performed in conformance with application commitments and without data to support DS suitability.
- A significant unresolved history of in-process testing results exceeding microbial action limits.
- Failure to conduct required adventitious agents testing, including mycoplasma and viral safety testing, in accordance with the BLA.
- Release of DS following a significant reprocessing step or a reworking operation that was neither approved in the application nor performed in accordance with an FDA-approved protocol.
- Failure of the quality unit to exercise oversight of the DS batch release.
- Serious data integrity concerns (e.g., apparent changes to records to make unacceptable released material appear acceptable).

### Noteworthy Deficiencies: Examples

#### Quality System

- Pattern of failure to conduct adequate investigations with appropriate CAPAs.
- Failure to conduct an appropriately thorough investigation when evidence suggests that the safety, purity, or potency of a released DS has been adversely impacted.
- Pattern of failure to appropriately review batch production records (e.g., releasing batches with open investigations).
- Pattern of failure to perform management review of process performance and product quality.
- Pattern of failure to review and approve changes in starting materials, facilities, support systems, equipment, manufacturing processes, laboratory methods, and container closure systems.
- Pattern of failure to review and approve SOPs, laboratory methods, and master batch records.
- Failure to notify FDA of a change requiring the submission of a prior approval supplement.
- Pattern of failure to notify FDA of changes requiring the submission of a CBE-30.
- Pattern of failure to appropriately file BPDRs for deviations with a significant possibility to affect the safety, purity, or potency of marketed product.

#### Facilities and Equipment System

- Failure to provide facilities and equipment that ensure consistent process performance.
- Failure to provide adequate facilities and equipment to ensure the prevention of contamination/cross-contamination.
- Repeated failures to appropriately maintain and calibrate instruments used to measure critical process parameters.
- Failure to properly maintain critical utilities or critical pieces of equipment such as WFI systems, fermenters/bioreactors, centrifuges, chromatography columns, and UF/DF equipment, especially if visually unacceptable, when likely associated with repeated bioburden or endotoxin action limit excursions, or when lack of maintenance leads to repeated deviations from approved process parameters.
- Failure to verify, when appropriate because of risk, the effectiveness of cleaning for shared equipment used to manufacture highly potent or toxic compounds.

#### Materials System

- Pattern of failure to adequately qualify critical raw material suppliers or monitor critical raw material quality.
- Pattern of failure to adequately evaluate changes to critical raw materials.
- Pattern of failure in raw material identification, inventory, or storage practices (including quarantine status failures).



**Production System**

- Pattern of failure to establish or follow adequate written procedures for production and process control.
- Pattern of failure to provide for production record traceability (e.g., multiple production records that do not attribute steps to unique individuals).
- Failure to protect production records from changes by personnel who are not authorized to make changes.
- Failure to provide a production record audit trail (electronic or otherwise).
- Failure to appropriately validate production processes, including failure to conduct requalification activities when appropriate.

**Laboratory Control System**

- Pattern of failure to ensure that laboratory raw data results match formally recorded results (e.g., those recorded on COAs).
- Pattern of failure to maintain complete and original (or complete true copies of) data, including relevant metadata.
- Pattern of failure to provide for laboratory record traceability.
- Failure to protect data, files, and systems from changes by personnel who are not authorized to make changes.
- Failure to provide for laboratory data change/manipulation audit trails.
- Pattern of failure to appropriately sample for in-process or final DS testing.
- Failure to establish an adequate OOS procedure.
- Pattern of failure to follow an established OOS procedure.
- Pattern of failure to provide justification for repeated testing.
- Failure to conduct testing as indicated in the BLA.
- Pattern of failure to perform tests in accordance with established procedures.
- Failure to properly validate/qualify critical test methods (methods designed to assess critical quality, safety, or efficacy attributes).
- Pattern of failure to adequately qualify contract testing laboratories.

**Packaging and Labeling System**

- Failure to package bulk DS in the approved container.
- Failure to properly label bulk DS containers.
- Pattern of failure to adequately investigate bulk DS leakage events.
- Failure to ship bulk DS according to established shipping procedures and application commitments.

### 3. Communications With Protein DS Manufacturers

Given the medical need for protein products, it is extremely important that FDA's action plans for noncompliant protein DS manufacturers are **proactive** and that they **stress communication**. Because the qualification of a new protein DS establishment is a lengthy process, a single establishment found to be unqualified to produce a DS of adequate quality can result in product shortage. Therefore, if CGMP deficiencies observed during an inspection (including those that identify **emerging** issues) threaten the quality and continued availability of these protein DS, FDA should seek to engage directly with senior management at the affected establishment as well as with global management officials, as appropriate. Accordingly, this communication is emphasized in the regulatory strategies outlined below. The level of communication/engagement may differ to some extent from that employed for a noncompliant manufacturer whose failures would not likely result in the extended shortage of medically needed products.

### 4. Potential Actions

When encountering CGMP noncompliant drug manufacturers, FDA may choose to do one or more of the following:

- Take no action.
- Hold a regulatory meeting (or meetings) with the manufacturer.
- Issue a warning letter (or other advisory notice).
- Issue an import alert (for foreign manufacturers).
- Recommend a voluntary product recall.
- Pursue a mandatory product recall.<sup>32</sup>
- Pursue product seizure.
- Pursue establishment injunction.
- Suspend product approval or licensing.
- Withdraw or revoke product approval or licensing (following the opportunity for a hearing or an opportunity to demonstrate compliance).
- Withhold the approval of pending applications and application supplements requiring an evaluation of the establishment.
- Invoke FDA's Application Integrity Policy.
- Pursue prosecution.
- Pursue the imposition of civil money penalties.

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<sup>32</sup> For licensed biologics, see section 351(d)(1) of the PHS Act.

## 5. Additional Expectations for Compliance Review

### A. Addressing Outstanding Insufficiencies

In accordance with the proactive approach described in Part V.3, if the insufficiency of one or more 483 responses has not been communicated to the firm through an advisory notice, it should be communicated through other means and a written commitment to implement appropriate CAPAs should be obtained and appropriately archived. To this end, COs must be certain to thoroughly evaluate the firm's 483 responses for **all** appropriate CAPAs as well as any interim mitigation steps that the firm implements while the firm is determining which CAPAs to take. COs should assess whether proposed timelines for implementation are appropriate and how the effectiveness of CAPAs will be verified. Additionally, if noteworthy deficiencies are identified through EIR review (i.e., deficiencies that were not cited on the 483), COs should likewise seek the firm's written commitment to implement appropriate CAPAs.

### B. Involvement of Product Specialists

Given the nature of the products covered by this compliance program, particularly their complexity of manufacture, relevant CDER product specialists should always be consulted if a regulatory action is being considered.

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

### 1. References

#### A. Acts

Biologics Price Competition and Innovation Act

Federal Food, Drug, and Cosmetic Act, sections 201, 501, 702, and 704

Food and Drug Administration Safety and Innovation Act, section 711

Patient Protection and Affordable Care Act, sections 7001 through 7003

Public Health Service Act, section 351

#### B. Code of Federal Regulations

<https://www.ecfr.gov>

9 CFR 113.53

21 CFR parts 600, 601, 610 (including §§ 600.3(h)(6), (s), and (w); 600.10(b)(3); 600.11(e)(3); 600.14; 600.80; 601.2; and 610.10)

#### C. Compliance Policy Guide

<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/manual-compliance-policy-guides>

CPG Sec. 130.300 *FDA Access to Results of Quality Assurance Program Audits and Inspections*

#### D. Compliance Programs

<https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs>

7346.832—Preapproval Inspections

7356.002—Drug Manufacturing Inspections

7356.002A—Sterile Drug Process Inspections

7356.002F—Active Pharmaceutical Ingredient (API) Process Inspection

#### E. FDA Guidances

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

**(1) Guidances for Industry**

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

*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)

*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)

*Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* (October 2006)

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

*Process Validation: General Principles and Practices* (January 2011)

*Pyrogen and Endotoxins Testing: Questions and Answers* (June 2012)

*Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006)

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

**Draft Guidances**

*CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports* (August 2017)

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

**(2) ICH Guidances for Industry**

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

*Q2A(R1) Text on Validation of Analytical Procedures* (March 1995)

*Q2B(R1) Validation of Analytical Procedures: Methodology* (May 1997)

*Q4B Annex 4A(R1) Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests General Chapter* (September 2010)

*Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin* (September 1998)

*Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products* (February 1996)

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

*Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* (September 1998)

*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)

*Q9 Quality Risk Management* (June 2006)

*Q10 Pharmaceutical Quality System* (April 2009)

*Q8, Q9, and Q10 Questions and Answers(R4)* (November 2011)

*Q8, Q9, and Q10 Questions and Answers—Appendix: Q&As From Training Sessions (Points to Consider for Q8, Q9, & Q10)* (July 2012)

*Q11 Development and Manufacture of Drug Substances* (November 2012)

*Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Questions and Answers* (February 2018)

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

#### F. FDA Procedures and References

*Guide to International Inspections and Travel*, <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/foreign-inspections>

*Guides to Inspection*, <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-guides>

- *Pharmaceutical Quality Control Labs*
- *Microbiological Pharmaceutical Quality Control Labs*
- *Validation of Cleaning Processes*
- *High Purity Water System*

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

*Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations (ConOps)*, <https://www.fda.gov/drugs/pharmaceutical-quality-resources/integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept-operations>

MAPP 5014.1 *Understanding CDER's Risk-Based Site Selection Model*,  
<https://www.fda.gov/media/118214/download>

*Regulatory Procedures Manual*, <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/regulatory-procedures-manual>

#### G. Non-FDA Standards and Reports

ANSI/AAMI ST72:2011(R2016), *Bacterial Endotoxins—Test Methods, Routine Monitoring, and Alternatives to Batch Testing*

ASTM E2281: Standard Practice for Process Capability and Performance Measurement

ASTM E2587: Standard Practice for Use of Control Charts in Statistical Process Control

ISPE Baseline Guide Volume 4 *Water and Steam Systems* (2011)

ISPE Baseline Guide Volume 7 *Risk-Based Manufacture of Pharmaceutical Products* (2010)

ISPE Good Practice Guide *Heating, Ventilation, and Air Conditioning* (2009)

ISPE Good Practice Guide *Process Gases* (2011)

PDA Technical Report No. 1 *Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control* (2007)

PDA Technical Report No. 13 (Revised) *Fundamentals of an Environmental Monitoring Program* (2014)

PDA Technical Report No. 14 *Validation of Column-Based Chromatography Processes for the Purification of Proteins* (2008)

PDA Technical Report No. 15 *Validation of Tangential Flow Filtration in Biopharmaceutical Applications* (2009)

PDA Technical Report No. 41 *Virus Filtration* (2008)

PDA Technical Report No. 49 *Points To Consider for Biotechnology Cleaning Validation* (2010)

PDA Technical Report No. 50 *Alternative Methods for Mycoplasma Testing* (2010)

PDA Technical Report No. 57 *Analytical Method Validation and Transfer for Biotechnology Products* (2012)

PIC/S PI 054-1, *How To Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management* (2021)

#### H. United States Pharmacopeia

<https://www.uspnf.com/>

Purified Water, USP

Water for Injection, USP

USP General Chapter <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*

USP General Chapter <63> *Mycoplasma Tests*

USP General Chapter <85> *Bacterial Endotoxins Test*

USP General Chapter <1072> *Disinfectants and Antiseptics*

USP General Chapter <1113> *Microbial Characterization, Identification, and Strain Typing*

USP General Chapter <1117> *Microbiological Best Laboratory Practices*

## 2. Attachments

Attachment A: Considerations for Protein Drug Substance Surveillance Inspections

Attachment B: Highly Potent or Toxic Products

Attachment C: Spore-Forming Microorganisms

## 3. Program Contacts

For technical questions concerning inspections, contact:

### **Office of Regulatory Affairs**

### **Office of Pharmaceutical Quality Operations/Division of Pharmaceutical Quality Programs**

301-796-2720

[ORAHQDrugInspectionPOC@fda.hhs.gov](mailto:ORAHQDrugInspectionPOC@fda.hhs.gov)

### **Office of Regulatory Science/Office of Medical Products, Tobacco, and Specialty Laboratory Operations**

Shari Kahn (Chemistry), 301-796-8154, [shari.kahn@fda.hhs.gov](mailto:shari.kahn@fda.hhs.gov)

Angele Smith (Microbiology), 301-796-4200, [angele.smith@fda.hhs.gov](mailto:angele.smith@fda.hhs.gov)

For technical questions concerning protein DS or product-specific questions, contact:

### **Office of Quality Surveillance**

[CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov)

[CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov)

(In urgent situations, call the relevant product specialist directly using contact information provided by CDER.)

For other questions, contact:

### **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, email the following address and it will be handled as a top priority:

[OPQPolicy@fda.hhs.gov](mailto:OPQPolicy@fda.hhs.gov)

**Enforcement-Related Guidance or Policy**

For enforcement-related guidance or policy, including evidence need and sufficiency, citations, and case evaluation/recommendation advice, email the following address and it will be handled as a top priority:

[CDEROMQCompliance@fda.hhs.gov](mailto:CDEROMQCompliance@fda.hhs.gov)

**Labeling Requirements and Policies**

For questions about labeling requirements and policies, contact the Office of Compliance's Office of Unapproved Drugs and Labeling Compliance via the office's intranet page: [CDER | Office of Compliance | Office of Unapproved Drugs and Labeling Compliance]

**Registration and Drug Listing Requirements**

For questions about registration and drug listing requirements, contact the Office of Compliance's Drug Registration and Listing contacts on the "CDER: Who's the Lead" intranet page:

[CDER | Office of Communications | CDER: Who's the Lead]

**4. Acronyms and Abbreviations**

483	Form FDA 483, Inspectional Observations
AAMI	Association for the Advancement of Medical Instrumentation
ADE	acceptable daily exposure
AER	adverse experience report
ANSI	American National Standards Institute
API	active pharmaceutical ingredient
BI	biological indicator
BLA	biologics license application
BPDR	biological product deviation report
CAPA	corrective and preventative action
CBE	change being effected
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations

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CGMP	current good manufacturing practice
CMS	Compliance Management System
CO	compliance officer
COA	certificate of analysis
DS	drug substance
EIR	establishment inspection report
EM	environmental monitoring
FACTS	Field Accomplishments and Compliance Tracking System
FD&C Act	Federal Food, Drug, and Cosmetic Act
HTST	high temperature short time
HVAC	heating, ventilation, and air conditioning
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (or <i>International Council for Harmonisation</i> )
ISPE	International Society for Pharmaceutical Engineering
LIMS	laboratory information management system
MCB	master cell bank
OAI	Official Action Indicated
OMPTO	Office of Medical Products and Tobacco Operations
OMQ	Office of Manufacturing Quality
OOS	out-of-specification
OPQ	Office of Pharmaceutical Quality
OPQO	Office of Pharmaceutical Quality Operations
OQS	Office of Quality Surveillance
ORA	Office of Regulatory Affairs
PACMP	postapproval change management protocol
PAI	preapproval inspection
PDA	Parenteral Drug Association
PHS	Public Health Service (Act)
PLCM document	Product Lifecycle Management document
PLI	prelicense inspection

pOAI	potential Official Action Indicated
PQS	pharmaceutical quality system
SOP	standard operating procedure
TSE	transmissible spongiform encephalopathy
UF/DF	ultrafiltration/diafiltration
USP	United States Pharmacopeia
WCB	working cell bank
WFI	water for injection

**PART VII—CENTER RESPONSIBILITIES**

See compliance program 7356.002, Part VII.

**Drug Shortages**

If violative conditions are identified that may result in a shortage, field staff should notify CDER drug shortage staff at [drugshortages@fda.hhs.gov](mailto:drugshortages@fda.hhs.gov) and ensure that the company also contacts CDER drug shortage staff. Notification should occur as soon as the division becomes aware of a possible shortage.

## ATTACHMENT A: CONSIDERATIONS FOR PROTEIN DRUG SUBSTANCE SURVEILLANCE INSPECTIONS

Attachment A contains questions that focus on the areas of highest risk in the six pharmaceutical manufacturing systems described in compliance program 7356.002 as well as additional questions that may be relevant to protein drug substance (DS) surveillance inspections.

◆ = critical questions for highest risk areas

◇ = additional, supplemental questions

Inspection teams should substantially cover the critical questions and are highly encouraged to consider all questions, particularly if the topics of the questions have not been covered in previous recent surveillance inspections.

The questions in this attachment do not constitute a comprehensive list of questions to cover during protein DS surveillance inspections. The inspection team should follow any line of questioning necessary to evaluate manufacturing and product quality.

The answers to these questions do not have to be reported in the establishment inspection report (EIR) unless they are relevant (e.g., negative answers may indicate a current good manufacturing practice (CGMP) deficiency). This approach informs and supports efficient, risk-based inspectional coverage.

### 1. Quality System

#### A. Senior Management Responsibility

- ◆ Has senior management ensured that the quality unit's authority and responsibilities are independent of production?
- ◆ Does senior management provide resources, including facilities, materials, equipment, personnel, training, and support systems, to ensure that each protein DS batch has the safety, identity, strength, quality, and purity that it purports or is represented to possess?
- ◆ Does senior management oversee the supply chain to ensure raw material suitability and ongoing reliability of suppliers?
- ◆ Does senior management ensure that outsourced operations (e.g., contract laboratory, contract manufacturing organization) are handled as an extension of the site's operation and that they fully conform with CGMP requirements?
- ◆ Does senior management ensure that the responsible parties/departments follow through on commitments to implement corrective and preventive actions (CAPAs)?

Supplemental questions:

- ◇ Does senior management encourage staff in all departments and at all levels to conduct work in a manner indicating that quality is a priority? Are staff given the proper degree of autonomy to respond to emerging issues and escalate major problems?
- ◇ Has senior management ensured that lifecycle quality risk management is integrated into the overall site operation?
- ◇ Has the firm appropriately implemented senior management review and documented management review meetings? Is the scope of management review well-defined, and does it include appropriate quality data and metrics?

B. Quality Unit

- ◆ Does the firm have a quality unit with appropriate documented responsibilities and procedures? Does the quality unit adhere to these responsibilities and follow these procedures? This includes, but is not limited to:
  - ◆ Approval of written production, quality control, and quality assurance procedures.
  - ◆ Review and approval of specifications, methods, processes, and master batch records.
  - ◆ Raw material and final protein DS batch release.
  - ◆ Change management.
  - ◆ Investigation and resolution of deviations and complaints.
- ◆ Are the firm's quality-related activities defined and documented? Is the quality unit involved in all quality-related decisions?
- ◆ Are procedures in place to promptly escalate issues to management in the event of serious CGMP deficiencies, product defects, and related issues?
- ◆ If the establishment functions as a contract manufacturer or outsources manufacturing or testing activities, are the responsibilities of the quality unit clearly established (e.g., in quality agreements or other appropriate agreements with applicants)?

C. Internal Audits

Supplemental question:

- ◇ Does the firm perform regular internal audits according to an approved, defined schedule; report results to responsible management; and complete CAPAs as appropriate?

## D. Process Performance and Product Quality Monitoring

### (1) Ongoing Program

- ◆ Does the firm monitor process performance and product quality throughout the year, and does it take appropriate action in response to operational variation or other quality concerns?
- ◆ Does the firm have and follow written procedures to periodically evaluate quality attribute in-process monitoring and testing results (e.g., step yields, impurities, microbial attributes), and does it respond appropriately to adverse trends?
- ◆ For each protein DS manufactured at the firm, does the firm's information about product quality and process monitoring/trending confirm that process performance is consistent and that acceptance criteria are consistently met? Information includes:
  - ◆ Column chromatography traces.
  - ◆ Monitoring/trending of step yields.
  - ◆ Monitoring/trending for relevant impurities from release and stability analysis.
  - ◆ Monitoring/trending of potency results from release and stability analysis.
  - ◆ Monitoring of in-process microbial quality.
  - ◆ Other attributes or measures of performance that provide information on process consistency.
- ◆ Does the firm increase monitoring in response to newly identified process failure modes?

#### Supplemental questions:

- ◇ Does the firm periodically review quality standards, specifications, and manufacturing or control procedures and implement needed changes?
- ◇ Does the firm have an ongoing program to monitor:
  - Facility and equipment suitability and performance.
  - Raw material variability.
  - Nonconformances, deviations, errors, and atypical events.
  - Product quality failures, quality anomalies, and out-of-specification (OOS) results.
  - Complaints, returns, and recalls.
  - Regulatory findings (local, or at another site in the supply chain).
  - Internal and external audits.
  - Record authenticity (data integrity)?

**(2) Annual Review**

- ◆ Does the firm have suitable written and approved procedures for conducting formal product quality reviews?
- ◆ Does the firm conduct adequate product quality reviews at least annually, maintain appropriate documentation for those reviews, and review and assess the results of the reviews in a timely manner? Do these reviews include assessments of the effectiveness and completion of CAPAs?
- ◆ Do the most recent product quality reviews for each protein DS manufactured at the establishment indicate that the DS have been consistently manufactured with sufficiently high quality? If not, has the firm taken appropriate actions to regain control?

## Supplemental question:

- ◇ Do the annual reviews include summary analyses covering, among other things:
  - Critical in-process control and release test results.
  - Batches failing to meet established specifications.
  - Critical deviations or nonconformances, OOS test results, and related investigations.
  - Changes carried out to manufacturing processes or analytical methods.
  - Stability monitoring program results.
  - Quality-related complaints, returns, and recalls.
  - The adequacy of implemented corrective actions.
  - Process performance/capability.
  - Trending of critical quality attributes?

**E. Change Management and Reporting**

- ◆ Does the firm have and follow suitable written and approved procedures for change management?
- ◆ Based on a review of select change management documentation, does the firm evaluate relevant changes for potential impact on product quality, and are changes reviewed and approved by appropriate organizational units?
- ◆ Does the firm ensure change effectiveness after changes are implemented? If there are indicators of product quality impact following manufacturing or testing changes, does the firm take appropriate and timely actions if needed?
- ◆ Does the firm report changes to FDA as required?



#### F. Validation and Verification Activities

- ◆ Does the firm conduct appropriate investigations and take appropriate actions in response to validation, verification, qualification, or requalification failures? Are appropriate CAPAs taken in a timely manner, particularly for failures indicating potential protein DS suitability issues?
- ◆ Does the firm evaluate if the filing of a biological product deviation report (BPDR) is necessary following validation, verification, qualification, or requalification? (See Part III.3.L—[Drug Quality Reports—BPDRs.](#))

#### Supplemental questions:

- ◇ Have validation efforts been appropriately conducted and documented and appropriate change management and reporting procedures been followed before those processes and methods are used to produce and test marketed products?
- ◇ Does the firm have and follow suitable written and quality unit-approved procedures for the validation and qualification of processes, test methods, equipment (including cleaning), and shipping? Are these procedures, if applicable, consistent with a lifecycle approach to process validation (see Part III.6.A(5)—[Process Validation](#))?

#### G. Stability Program

- ◆ Does the firm have and follow suitable written and approved procedures for its stability program?
- ◆ Does the firm adhere to the stability testing commitments made in relevant biologics license applications (BLAs), and does it perform additional testing if needed to respond to lifecycle events?
- ◆ If applicable, does the firm adequately investigate and document stability failures or adverse stability trends, performing appropriate CAPAs in a timely manner? Are investigations extended to other batches as necessary?
- ◆ Does the firm evaluate if the filing of a BPDR is necessary for potential stability issues? (See Part III.3.L—[Drug Quality Reports—BPDRs.](#))

#### H. Deviation and Failure Investigations

- ◆ Does the firm have and follow suitable written and approved procedures for handling investigations? Do procedures include appropriate involvement of the quality unit, such as the responsibility for ensuring adequate resolution of investigations?
- ◆ Does the firm investigate thoroughly and respond adequately to deviations and failures?
- ◆ If there are adverse trends, does the firm adequately investigate and address them as appropriate?

#### I. Rejected/Aborted and Reprocessed Batches

- ◆ Are appropriate investigations conducted for rejected/aborted batches?
- ◆ Do records confirm that rejected batches (if any) are properly disposed of and not released for distribution?
- ◆ Are there discrepancies between the number of batches initiated and the number of batches completed (i.e., there are failures to successfully manufacture batches from each cell bank thaw)? Are there repeated failures to successfully manufacture batches? Does the firm adequately investigate these failures?

#### J. Complaints and Adverse Experience Reports

- ◆ Does the firm have and follow suitable written and approved procedures for handling complaints and adverse experience reports (AERs)?
- ◆ Does the firm maintain appropriate documentation for the management and review of complaints and AERs?
- ◆ Does the firm adequately investigate complaints and AERs related to protein DS quality, taking appropriate and timely actions?

#### K. Returns

- ◆ If appropriate, does the firm investigate returned material? Does the firm take appropriate and timely actions if there are indicators of possible protein DS suitability issues?
- ◆ Is adequate control maintained over returned protein DS to ensure suitability for use if not intended for destruction (e.g., cold chain controls and other controls to ensure the material is of acceptable quality)?
- ◆ Does the firm make acceptable decisions regarding the restocking of returned protein DS?

#### Supplemental question:

- ◇ Does the firm have and follow suitable written and approved procedures regarding the handling of returns (if applicable)?

#### L. Drug Quality Reports—BPDRs

- ◆ If there were BPDRs applicable to this establishment for the time period evaluated, did the firm conduct appropriate investigations and take appropriate actions in response to the event/deviation that triggered the reporting?
- ◆ Are BPDRs submitted appropriately for reportable events?

Supplemental question:

- ◇ Does the firm have and follow suitable written and approved procedures for the handling of reportable events?

M. Quarantined Protein DS

- ◆ Does the firm have and follow suitable written and approved procedures for the release of protein DS? Are these release procedures consistent with BLA release criteria?

Supplemental questions:

- ◇ Does the firm reach disposition decisions on all protein DS batches within a reasonable time frame? If not, does the firm have an adequate justification for why batches or intermediates have not been either released or rejected in a timely manner?
- ◇ Are the firm's protein DS (quarantined and released) storage areas suitable, including for the prevention of deterioration and contamination?

N. Recalls

- ◆ Does the firm have and follow suitable written and approved procedures regarding the recall of its protein DS?
- ◆ If there were recalls related to the quality of protein DS for the time period evaluated, did the firm conduct appropriate investigations and take appropriate actions as a result of the recall? If recalls related to quality were for batches distributed only in foreign markets, were the quality issues evaluated for potential impact to U.S.-marketed product?
- ◆ If recalled protein DS batches were used to manufacture distributed drug product, was the affected drug product recalled? (If the protein DS manufacturer does not know, the inspection team should email relevant information to [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and should cc: [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov).) If the protein DS manufacturer is also the applicant, did it submit a BPDR within the required time frame? (See Part III.3.L—[Drug Quality Reports—BPDRs](#).)

O. Data Integrity

- ◆ If the firm has more than one manufacturing or testing record for the same activity and lot **and** the records contain differences indicating that processes strayed beyond established limits or test results were OOS or out of trend, does the firm have a reasonable explanation?
- ◆ Does the firm refrain from the practice of testing different samples until the desired passing result is achieved (i.e., does it avoid testing into compliance)?
- ◆ Are records documented contemporaneously with the performance of operations (manufacturing or testing)? Are dates, times, and initials indicated for each process step? For electronic records, are data saved promptly after entry (as opposed to personnel performing

several steps then simultaneously saving data from those steps)? Are system users restricted from changing system date and time stamps?

- ◆ Does the firm review **complete** original records or true copies (not just transcribed data or summaries of results)?
- ◆ Are electronic data appropriately reviewed, including metadata such as audit trails?

Supplemental questions:

- ◇ Are CGMP records appropriately initialed and signed (i.e., traceable to a unique individual)? For electronic records, are **unique** login user IDs used in place of initials and **appropriately controlled** electronic signatures used in place of handwritten signatures?
- ◇ Are standard operating procedures (SOPs) written and electronic systems designed to prevent changes to records unless the changes have been documented? Do electronic systems prevent data obscuration with annotation tools? Do justifications for record changes contain enough information to understand the reason for the change? (The inspection team should question frequent changes annotated simply as *entry error*.) Are CGMP record changes captured in an audit trail?
- ◇ Are electronic records or true copies protected from overwriting and deletion?
- ◇ Does the firm report all test results on quality control testing records (as opposed to selectively reporting results)?
- ◇ Does the firm retain original records (or complete true copies of original records) with appropriate record retention timelines? Do these records contain **all** first-capture CGMP data and all metadata needed to reconstruct CGMP activity? (For systems such as chromatography data systems, this includes data collected and files indicating the handling of such data, e.g., raw data, results, methods, audit trail files.)
- ◇ Are computerized records management systems designed and validated for intended use to ensure the integrity and accuracy of data entered and the proper handling, transferring, and maintenance of such data (i.e., to ensure good documentation practices)?
- ◇ Do electronic systems have appropriate security access permissions? Are users prevented from changing system configurations and from moving, deleting, or altering files?

## 2. Facilities and Equipment System

### A. Equipment

#### (1) General

- ◆ Is equipment of appropriate design and construction?
- ◆ Is equipment suitable for its intended use in the process?

- ◆ Are the physical setup of equipment and equipment connections appropriate and is the equipment free from leaks (if applicable)?
- ◆ Is the firm's equipment maintained in good working condition?
- ◆ Is equipment identified as to its contents and cleanliness status by appropriate means?
- ◆ Does the firm maintain appropriate records for the cleaning, sterilization/sanitization (if applicable), and use of critical pieces of equipment?
- ◆ Does the firm adequately investigate and document failures related to critical pieces of process equipment (e.g., fermenters/bioreactors, purification columns, ultrafiltration/diafiltration (UF/DF) equipment, viral clearance/inactivation equipment, sterilizers), performing appropriate CAPAs in a timely manner?
- ◆ If there have been recent changes to critical pieces of equipment, did the firm evaluate the changes for their potential impact on product quality, and were they reviewed and approved by appropriate organizational units and submitted to FDA as appropriate?

## **(2) Equipment Qualification and Requalification**

- ◆ Has the firm appropriately qualified newly added equipment?
- ◆ If necessary, has the firm appropriately requalified equipment following major changes to the equipment or its implication/potential implication in recent manufacturing deviations or failures?

### Supplemental question:

- ◇ Are key pieces of equipment, such as those listed below, suitable for their intended use as demonstrated through appropriate monitoring, periodic review of the qualified state, and requalification (as needed)?
  - Fermenters/bioreactors.
  - Centrifuges or other harvest equipment.
  - Purification skids.
  - UF/DF skids.
  - Autoclaves.
  - Equipment used for high temperature short time (HTST) treatment of cell culture media.

## **(3) Equipment Maintenance and Calibration**

- ◆ Does the firm have and follow appropriate written and approved procedures for the periodic evaluation of equipment, including evaluation for corrosion, rouging, and the replacement of consumables (e.g., elastomers—gaskets, O-rings, and diaphragm valves)?

- ◆ Does the firm take appropriate and timely actions in response to identified equipment issues?
- ◆ Has the firm appropriately maintained pieces of equipment potentially implicated in recent manufacturing deviations or failures?
- ◆ Does the firm have and follow adequate procedures and schedules for maintaining equipment used in its manufacturing processes, such as those listed below, and does it retain appropriate documentation of maintenance?
  - ◆ Fermenters/bioreactors (including the changing of elastomer seals/gaskets).
  - ◆ Centrifuges or other harvest equipment.
  - ◆ Purification skids and associated columns.
  - ◆ UF/DF skids.
  - ◆ Autoclaves.
  - ◆ Equipment used for the HTST treatment of cell culture media.
- ◆ Are instruments, especially those used to measure or monitor critical in-process parameters (e.g., pH, dissolved oxygen), maintained and calibrated at appropriate intervals using appropriate standards? Do calibration procedures contain limits for accuracy over the relevant range and limits for precision as appropriate?
- ◆ If applicable, are the forms used to document equipment calibrations controlled?

#### **(4) Equipment Cleaning**

- ◆ Does the firm have appropriate cleaning validation or verification for equipment that is not product-dedicated?
- ◆ Are the frequency and scope of the firm's continued process verification for equipment cleaning adequately described and justified? Are the data for the firm's continued process verification acceptable?
- ◆ For equipment on which the firm has not yet completed cleaning validation, does the firm demonstrate that the equipment is clean before use through cleaning verification?
- ◆ Are the forms used to document equipment cleaning adequately controlled?

#### Supplemental questions:

- ◇ Has the firm appropriately listed equipment that should be cleaned?
- ◇ Has the firm described the cleaning processes to be used on different equipment (e.g., clean-in-place, clean-out of-place, manual washing, automated glass washer)?
- ◇ Do the firm's validated equipment cleaning procedures contain sufficient details for operators to reproducibly and effectively clean equipment, including instructions for disassembling and reassembling each piece of equipment if appropriate?

- ◇ Has the firm established procedures to ensure that clean equipment is stored in a dry location and is protected from contamination?
- ◇ During production, does the firm routinely visually inspect each piece of equipment after cleaning and before use whenever feasible?
- ◇ Does the firm adhere to its validated equipment dirty- and clean-hold times during production? Does the firm have procedures to handle exceeded hold times?

### **(5) Equipment Sanitization and Sterilization**

- ◆ If the firm experienced in-process bioburden/endotoxin levels above action limits, did it evaluate the effectiveness of sanitization/sterilization processes as part of its investigation and did it fully address identified sanitization/sterilization deficiencies?
- ◆ If there have been recent changes to sanitization/sterilization equipment or processes, did the firm evaluate the changes for their potential impact on product quality, and were they reviewed and approved by appropriate organizational units? Did the evaluation include assessing the need for sterilization/sanitization revalidation?
- ◆ If the firm validated sterilization processes after acquiring new equipment, did it place biological indicators (BIs) and thermocouples in worst-case locations during validation? Was the BI population verified for each BI lot? Were BIs used in strict accordance with vendor recommendations? If not, are the firm's BI decimal reduction value (D-value) verification data acceptable?
- ◆ If the firm experienced a contamination event but does not routinely conduct post-use integrity testing of equipment vent filters within sterile boundaries, was filter failure appropriately assessed as part of the root cause investigation?

#### Supplemental questions:

- ◇ Does the firm appropriately sterilize product-contact cell culture equipment or appropriately sterilize or sanitize fermentation equipment (or other equipment) before use?
- ◇ Does the firm adhere to established maximum sterilization/sanitization hold times during production, and does it have adequate procedures to handle exceeded hold times?
- ◇ Does the firm periodically evaluate its equipment sterilization/sanitization processes to verify that they are still operating as validated? If appropriate, are sterilize-in-place systems or processes requalified, with sufficient coverage of hard-to-sterilize areas (e.g., spargers, sampling lines)? Does the firm have adequate acceptance criteria and data for requalification work performed for the sterilization of bioreactors, addition tanks, and small parts?

**(6) Disposable Equipment**

- ◆ If the firm has records (e.g., deviation reports) that indicate recurring, unresolved issues with disposable container leakage, has it evaluated the issues and implemented appropriate CAPAs?
  - ◆ Does the firm handle disposable container leakage deviations in accordance with an approved SOP?
  - ◆ Are contamination and cross-contamination included in the impact and disposition evaluations for buffers, media, cell cultures, in-process intermediates, or final protein DS impacted by containers or equipment that have leaked?
  - ◆ Are root causes determined and CAPAs adequately implemented to prevent future leakage?

**(7) Computerized Systems**

- ◆ Are the firm's critical computerized systems—including those used in production, for material handling, for weighing and dispensing, and for laboratory operations—appropriately qualified or validated?
- ◆ Is the quality unit sufficiently involved in validation efforts for computerized systems?

**Supplemental questions:**

- ◇ If there have been recent changes to computerized systems, were they adequately controlled and qualified or validated as appropriate?
- ◇ Are appropriate controls exercised over computerized systems to prevent unauthorized access or changes to data? Are controls in place to prevent omissions in data?
- ◇ Is there a record of data changes made, including who made the changes and when?
- ◇ Are the computerized system's inputs and outputs checked for accuracy at a degree and frequency based on the complexity and reliability of the system?

**B. Facilities****(1) Water**

- ◆ Is the water used by the firm suitable for its intended use?
- ◆ Does the firm's water for injection (WFI) meet compendial (United States Pharmacopeia (USP)) standards (e.g., chemical and microbiological attributes)?
- ◆ Does the firm have and follow adequate procedures for sampling and testing water? Are the sampling locations and frequency appropriate given the water's intended use?



- ◆ Has the firm set appropriate alert and action levels for bioburden and endotoxin (where appropriate)? Does the firm appropriately investigate water action limit excursions? If applicable, is product impact adequately assessed following excursions?
- ◆ Has the firm appropriately addressed routine low-level (e.g., below alert level) bioburden recoveries from its WFI systems?
- ◆ Does the firm have suitable written and approved procedures for the periodic evaluation of water quality testing results? Does the firm follow these procedures and respond appropriately and in a timely manner to identified issues or adverse trends? Do trend data for water quality specifications indicate that the firm's water systems are operating in a continuous state of control?
- ◆ If there have been recent changes to WFI or purified water systems, did the firm evaluate the changes for their potential impact on product quality, and were they reviewed and approved by appropriate organizational units?
- ◆ Are water systems requalified, as appropriate (e.g., following major changes or implication in manufacturing deviations)?
- ◆ Does the firm have appropriate microbial action/alert levels for purified water based on USP standards? Are the action/alert levels periodically evaluated and adjusted as necessary?

Supplemental questions:

- ◇ Does the water used to feed water systems meet Environmental Protection Agency or comparable potable drinking water standards as directed in the USP? Does the firm conduct periodic testing to confirm this?
- ◇ Are the firm's water systems acceptably maintained and free from leaks?
- ◇ Does the firm have and follow adequate procedures for the maintenance of water systems? Do procedures cover the maintenance of pipes and pumps? Is the system routinely passivated? Are all components of the firm's water treatment systems (e.g., sand filters, carbon filters, deionizing units, reverse osmosis units) maintained adequately and periodically monitored to ensure proper performance?
- ◇ Are water systems appropriately and consistently sanitized?
- ◇ Does the firm adequately ensure that WFI system hot loops and storage tanks are maintained at appropriate temperatures, and does it take appropriate actions if they are not?
- ◇ Are the vent filters for WFI systems periodically tested for integrity and replaced? Is the frequency of replacement adequate? Are the integrity tests appropriately conducted?
- ◇ Are instruments used for routine in-line monitoring of water attributes appropriately maintained and calibrated?

**(2) Process Gases**

- ◆ Do process gases meet appropriate specifications, including those for identity and purity?
- ◆ Are product-contact process gases (including air used to dry equipment) periodically sampled and monitored for particulates, moisture, oil, and bioburden? Are the results acceptable?

## Supplemental questions:

- ◇ Are gas production systems sufficiently maintained?
- ◇ Are gas production systems requalified as appropriate, such as following any major system change?
- ◇ Do the firm's testing data and periodic evaluation/trending of test results indicate that gas production systems are capable of consistently producing gases of suitable quality?
- ◇ Are the sampling frequency, sampling points, testing methods, and alert or action limits for the firm's process gas monitoring program adequate?
- ◇ Are process gases sterile-filtered at the point of use for cell culture/fermentation processes? Is post-use integrity testing performed for gas filters used within sterile boundaries? If not, and if there were any contamination events, was filter failure adequately assessed as a potential root cause during the investigation?
- ◇ Is the replacement frequency for downstream process, product-contact, point-of-use gas filters appropriate and justified, for example, by post-use integrity test data?
- ◇ If the firm shares a compressed air system intended to be an oxygen source for cell culture and also actuate mechanical equipment (e.g., valves), does the firm have adequate surveillance to prevent the introduction of contaminants (microbial, particulate, solvents, or lubricants) when there is maintenance or there are repairs on system equipment?

**(3) Clean Steam**

- ◆ Does clean steam (if used) routinely fall within microbial monitoring alert or action limits? Are excursions appropriately investigated?

## Supplemental questions:

- ◇ Is the firm's clean steam system appropriately maintained and free from visible leaks?
- ◇ Has the firm set appropriate specifications for clean steam, in line with USP specifications for WFI?
- ◇ If there have been recent changes to clean steam generation systems, did the firm evaluate the changes for their potential impact on product quality, and were they reviewed and approved by appropriate organizational units?

#### (4) HVAC Systems

- ◆ If there have been recent changes to heating, ventilation, and air conditioning (HVAC) systems, did the firm evaluate the changes for their potential impact on product quality, and were they adequately qualified, reviewed, and approved by appropriate organizational units?

##### (a) Area Pressure Differentials

- ◆ Does the firm routinely monitor pressure differentials for clean areas, in particular to maintain segregation of live cell and cell-free areas and pre- and post-viral areas and to protect open operations? Do pressure differential data demonstrate that the pressure differentials between different areas are adequately maintained?
- ◆ Does the firm have an alarm system to alert it to inadequate pressure differentials? Does the firm appropriately respond to and investigate such alarms?

##### (b) Air Filters

###### Supplemental questions:

- ◇ Does the firm have an acceptable air filter recertification program and is recertification conducted at an adequate frequency? Does the program include critical areas such as biological safety cabinets? Does recertification testing include appropriate filter integrity and air velocity testing?
- ◇ Are the firm's recent filter recertification results acceptable or, in the case of recertification failure, did the firm take appropriate actions?
- ◇ If the firm uses biosafety cabinets or laminar flow hoods for open-step aseptic operations (e.g., sterile subassemblies and nutrient feed assemblies), are there procedures to ensure the equipment is returned to service after air handling systems are shut down?

#### (5) Facility Cleaning and Disinfecting

###### Supplemental questions:

- ◇ Are the firm's facility cleaning and disinfecting SOPs adequately specific to ensure that cleaning and disinfecting occur reproducibly, and do they include cleaning schedules, methods, and locations?
- ◇ Do all disinfectant solutions have an established expiry date?
- ◇ Does the firm periodically use appropriate sporicidal agents to control spores?
- ◇ Do the firm's training records indicate that personnel who clean and disinfect are adequately trained and supervised?

**(6) Facility Environmental Monitoring**

- ◆ Do the firm's environmental monitoring (EM) data and trend reports indicate that HVAC control and facility cleaning and sanitization programs are adequate and effective?
- ◆ If applicable, does the firm adequately investigate and document discrepancies and failures related to EM excursions, performing appropriate CAPAs in a timely manner? Do root cause investigations of viable action level excursions include the identification and evaluation of the potential origin of isolated microorganisms?

## Supplemental questions:

- ◇ Does the firm's EM program include monitoring of viable and nonviable air particulates as well as surfaces as appropriate?
- ◇ Does the firm's EM SOP describe the methods of sampling, sampling locations and frequencies, alert and action limits, and actions taken if limits are exceeded? Are the EM alert and action limits appropriate for area classifications and types of operations?
- ◇ Is the firm's EM frequency adequate for all stages of production and commensurate with the area classification and the types of operations conducted in each area (i.e., downstream operations monitored more frequently than upstream, open operations monitored more frequently than closed)? Is EM sampling performed during dynamic conditions?
- ◇ Does the firm periodically evaluate EM data and respond appropriately to adverse trends?
- ◇ Are the firm's facility microbial isolates periodically identified to determine the continued effectiveness of the facility disinfecting agents?

**(7) Pest Control**

- ◆ Are the firm's trap inspection frequency and pest monitoring limits adequate? Do the firm's monitoring data indicate appropriate control of pests?
- ◆ Does the firm conduct investigations and implement CAPAs that adequately address pest control deviations?

## Supplemental questions:

- ◇ Are raw materials protected from rodents and other pests that could carry adventitious agents?
- ◇ Are the locations and numbers of the traps inside and outside the facility adequate to prevent the contamination of the facility, equipment, raw materials, and products by pests?
- ◇ Does the firm have suitable written and approved procedures for the periodic evaluation of monitoring data? Does the firm follow these procedures and take appropriate and timely actions in response to identified adverse trends?

### C. Cross-Contamination Prevention

- ◆ If the firm engages in campaign-based manufacturing, does it effectively minimize the risk of cross-contamination and mix-ups, using effective end-of-campaign product changeover procedures and other procedural controls?
- ◆ Does the firm have adequate changeover procedures to prevent the mix-up and cross-contamination of raw materials, equipment, products, and so forth? Specifically,
  - ◆ Are changeover processes documented in sufficient detail? Are shared equipment and areas cleaned and released for use in accordance with procedures approved by the quality unit?
  - ◆ Is cleaning verification conducted for products for which cleaning validation has not been completed?
  - ◆ Are the firm's changeover records and cleaning verification data (if applicable) for previous changeover processes adequate?
- ◆ Does the firm have and follow adequate procedures to govern the flow of products, raw materials, personnel, waste, and equipment to prevent cross-contamination? If there are potential crossover points that could allow for cross-contamination between different products, between upstream and downstream steps, or between pre- and post-viral steps in the same process, has the firm adequately controlled these crossover points, if appropriate?
- ◆ For equipment shared among different products, do data for cleaning verification or requalification (if appropriate) meet the predetermined product residue carryover limits? For new products, was the criteria for product residue carryover limits met during cleaning validation?
- ◆ In the equipment washing area, does the firm segregate:
  - ◆ Soiled and clean equipment?
  - ◆ Cell culture and purification equipment?
  - ◆ Pre- and post-viral equipment?
  - ◆ Dedicated equipment from nondedicated equipment?
- ◆ If the firm has concurrent manufacturing operations, are they appropriately controlled to prevent cross-contamination?

#### Supplemental questions:

- ◇ Are personnel working in multiple areas trained on the proper passage between areas to prevent cross-contamination? If appropriate, does the firm require gowning changes when passing from one area to another?
- ◇ Does the firm have adequate procedures for handling contaminated process streams to ensure adequate containment?

### 3. Materials System

#### A. Sourcing and Vendor Qualification

- ◆ Do purchased materials meet appropriate written specifications approved by the firm's quality unit?
- ◆ Does the firm have an adequate procedure for selecting, qualifying, and monitoring raw material suppliers? Does monitoring include periodic communication with and auditing of suppliers?
- ◆ Has the firm adequately qualified recently added raw material suppliers, including disposable equipment suppliers?
- ◆ If the firm relies on certificates of analysis (COAs) as assurance that material specifications have been met (in lieu of testing every lot of material for conformance), does its procedure for the initial and ongoing re-evaluation/requalification of suppliers include verifying supplier test results at appropriate intervals?
- ◆ If there have been recent changes in the supply of critical raw materials, were those changes handled according to established and appropriate change management procedures? (See also Part III.3.E—[Change Management and Reporting](#).) Did the firm evaluate the changes for their potential impact on product quality, and were they reviewed and approved by appropriate organizational units? Were the changes reported to FDA, as appropriate?
- ◆ If used as a material in the formulation of bulk protein DS, is human serum albumin U.S.-licensed or approved in relevant BLAs?

#### Supplemental question:

- ◇ Does the firm ensure appropriate sourcing of high-risk raw materials?

#### B. Receipt, Inventory, and Storage of Materials

- ◆ Are materials stored under conditions (e.g., light, temperature, moisture) that are appropriate to prevent deterioration and contamination, microbial or otherwise?

#### Supplemental questions:

- ◇ Does the firm have and follow written procedures for the receipt and identification of materials?
- ◇ Does the firm ensure that disposable equipment is unpacked and handled in a manner that does not potentially damage its integrity (e.g., protected from sharp tools, handled to avoid the kinking of flexible tubing)?
- ◇ Does the firm maintain records (including identity, quantity, and manufacturer) of each received shipment of each batch of raw materials, intermediates, containers, closures, and labeling?

- ◇ Does the firm have and follow written procedures for the inventory and storage of materials?
- ◇ Are material storage areas of suitable size and design to allow for adequate cleaning and maintenance?

### C. Testing, Examination, and Release of Materials

- ◆ Does the firm confirm that received materials meet product specifications through testing or through examination of COAs from appropriately qualified vendors?
- ◆ Does the firm or material vendor test raw materials of animal origin for bacteria, fungi, mycoplasma, and other adventitious agents in accordance with 9 CFR 113.53 if those materials are not sterilized by heat sterilization or other methods acceptable to the U.S. Department of Agriculture's Animal and Plant Health Inspection Service?
- ◆ If applicable, does the firm conduct testing for adventitious agents as described in relevant BLAs?
- ◆ Does the quality unit release materials/components in accordance with established written procedures?
- ◆ Are appropriate expiry or retest dates assigned to materials?

#### Supplemental questions:

- ◇ Does the firm confirm through testing the identity of materials received? If not, is the firm able to provide appropriate justification for not doing so?
- ◇ Does the firm ensure that containers, closures, and labeling materials conform to established specifications, and does it reject those materials if they do not?
- ◇ Does the firm appropriately control rejected materials to prevent use?
- ◇ Does the firm maintain records tracing its use of each shipment of each batch of raw materials, intermediates, containers, closures, and labeling?
- ◇ Does the firm have and follow an appropriate procedure controlling the order in which material lots are used?

### D. Cell Banks

- ◆ Do the firm's freezer maintenance activities provide adequate assurance of cell bank protection? Do freezer temperature logs demonstrate that cell banks are being appropriately maintained?
- ◆ If the firm created and is using new working cell banks (WCBs) for approved products since the last inspection, did it report these WCBs as a supplement to the application or create and qualify them in accordance with an FDA-approved protocol and reporting strategy?

- ◆ Does the firm maintain records tracing the use of WCB vials (i.e., from removal from storage to completed or failed manufacturing campaigns)?
- ◆ Does the firm appropriately investigate whether manufacturing campaign failures correlate with WCB problems?

Supplemental questions:

- ◇ Does the firm have procedures for storing and handling cell banks?
- ◇ Does the firm limit cell bank access to authorized personnel?
- ◇ For cell lines used in manufacturing, does the firm adequately segregate (physically or otherwise) different cell lines to prevent mix-ups?
- ◇ Does the firm adequately segregate cell lines used for production and those that are either uncharacterized or quarantined, such as cell lines lacking testing results for adventitious agents?
- ◇ Does the firm have an adequate alarm system for cell banks (e.g., for temperature and liquid nitrogen level alarms)?
- ◇ If cell lines used in production are received from other establishments, is the firm able to demonstrate that cell lines are appropriately temperature-controlled during shipping?
- ◇ Does the firm have more than one storage location for cell banks to prevent catastrophic loss?
- ◇ Does the firm appropriately identify cell bank lots with at least a lot number and date of preparation? Does the firm maintain records that track which cell bank was used to initiate a production batch?
- ◇ Do stability reports indicate cell bank stability?

#### 4. Production System

##### A. General

##### (1) Personnel

Supplemental questions:

- ◇ Does the firm provide for an adequate number of personnel with appropriate background for its production operations?
- ◇ Does the firm have appropriate procedures (e.g., those governing gowning, hygiene, behavior, health) to protect the product from contamination by personnel?

##### (2) Master and Batch Production Records

- ◆ Does the firm conduct unit operations according to its batch instructions/records?



- ◆ On the basis of risk (e.g., deviation information), the inspection team should select and review appropriate batch record sections. Is information from each unit operation appropriately recorded?

### **(3) In-Process Sampling and Controls**

- ◆ Are in-process limits and sampling times/points appropriate for monitoring the process and consistent with relevant BLAs?

### **(4) Excursions, Deviations, and Failures**

- ◆ Are in-process test results within approved limits? If in-process limits were exceeded, including microbial/endotoxin action limits, did the firm conduct appropriate, timely, scientifically based investigations; identify actual or potential root causes; and implement appropriate CAPAs? Were the firm's product impact evaluations adequate and its product dispositions appropriate?
- ◆ Does the firm appropriately investigate production deviations and failures? (See also Part III.3.H—[Deviation and Failure Investigations](#).) The inspection team should focus on:
  - ◆ Deviations indicating recurring problems or trends.
  - ◆ Deviations with significant potential to impact product quality, such as deviations related to the clearance of product- and process-related impurities, viral clearance/inactivation deviations, and bioburden and endotoxin control deviations.

### **(5) Process Validation**

- ◆ If concurrent validation activities are ongoing or were completed in the time since the last CGMP surveillance inspection, do the interim or final reports for these activities indicate acceptable control?
- ◆ Does the firm conduct continued process verification, as appropriate, consistent with a lifecycle approach to process validation? If not, is the firm's rationale for lack of continued process verification adequate?
- ◆ Does the firm have pending change management activities that may be indicative of incomplete/inadequate process validation?

Supplemental question:

- ◇ Are the firm's validation reports and protocols reviewed and approved by the quality unit?

### **(6) Reworking and Reprocessing**

- ◆ For steps meeting the definition of reworking in International Council for Harmonisation (ICH) guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, does the firm:

- ◆ Conduct an appropriate investigation before reworking?
- ◆ Complete an adequate risk assessment for its reworking activities?
- ◆ Appropriately evaluate reworked batches to ensure that product quality has not been compromised, including, if necessary, using additional analytical test methods and stability testing?
- ◆ Submit reworked batches to FDA for approval before release (unless it releases the batches **under quarantine** and is seeking FDA approval for the reworking)?
- ◆ Provide evidence that the reworking activities have been communicated to FDA in a timely manner through a submission? (If no, communicate this finding immediately to [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc: [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov).)
- ◆ If applicable, does the firm reprocess released protein DS (or DS intended to be released) in accordance with the product's approved procedures? If not sure or there is a concern, email the details of the reprocessing steps to [CDERBIOTECHINSPECT@fda.hhs.gov](mailto:CDERBIOTECHINSPECT@fda.hhs.gov) and cc: [CDERSurveillance@fda.hhs.gov](mailto:CDERSurveillance@fda.hhs.gov).)
- ◆ If applicable, does the firm adequately investigate and document discrepancies and failures that prompt reprocessing steps not covered by the BLA, performing appropriate CAPAs in a timely manner?

Supplemental questions:

- ◇ Does the firm have and use suitable written procedures for reprocessing steps?
- ◇ Have reprocessing steps, if any, been appropriately justified through validation studies? If validation studies are still being conducted, do interim data demonstrate process control?
- ◇ For batches manufactured using reprocessing steps, are the batches acceptable based on batch records or testing results?

B. Weighing and Dispensing of Materials

- ◆ Are the firm's changeover procedures that describe steps to take between handling different raw materials adequate to prevent cross-contamination?

Supplemental questions:

- ◇ Does the firm have complete and accurate SOPs for tracking and weighing materials?
- ◇ Does the firm accurately record weighing and dispensing information in batch records?
- ◇ Does the firm have secondary sign off (if applicable) for procedures involving the weighing, dispensing, and addition of materials?

### C. Media and Buffer Preparation and Holding

- ◆ Does the firm use the buffers and media defined in relevant BLAs in production? Are the media and buffers accurately described in the master batch records?
- ◆ If applicable, does the firm adhere to the validated parameters (e.g., temperature, time, flow rate) during cell culture media HTST treatment?

#### Supplemental questions:

- ◇ Does the firm have adequate procedures for preparing, labeling, storing, and tracking buffers and media?
- ◇ Does the firm appropriately calibrate instruments used for buffer and media preparation? (See also Part III.4.A(3)—[Equipment Maintenance and Calibration](#).)
- ◇ Is the firm's cell culture media preparation process closed or safeguarded with the use of adequate environmental and procedural controls?
- ◇ Does the firm adhere to predefined and validated hold times and conditions for buffers and media?
- ◇ Do the firm's buffers meet their defined limits, including endotoxin, if applicable?

### D. Cell Culture and Production-Scale Expression

- ◆ Does the firm appropriately investigate instances of a WCB failing to generate the growth necessary for production?
- ◆ Are production fermenter/bioreactor parameters such as dissolved oxygen, pH, cell density, and so forth monitored per the approved application? Are excursions appropriately evaluated?
- ◆ If applicable, does the firm adequately investigate and document fermenter/bioreactor process discrepancies or failures, performing appropriate CAPAs in a timely manner?
- ◆ Do the firm's fermenter/bioreactor growth profiles and titers from production runs indicate consistent process performance? If not, has the firm adequately investigated inconsistencies and taken appropriate CAPAs if necessary?
- ◆ Is the firm's success rate for production runs (starting from cell bank thawing) adequate?
- ◆ Do the bioburden data for cell culture processes meet the bioburden limits specified in BLAs? Does the firm have procedures to determine the course of action if contamination is confirmed? Is the impact of contamination on the product assessed and considered in determining disposition?
- ◆ Are the firm's unprocessed bulk safety tests (e.g., viral testing, mycoplasma, bioburden), including assays and acceptance criteria, consistent with relevant applications?

Supplemental questions:

- ◇ Does the firm have and follow procedures for maintaining and expanding cell cultures, and does it keep appropriate records for these activities? Are cell passage numbers consistent with end-of-production studies or limits of in vitro cell age as identified in relevant BLAs? Does the firm have appropriate controls to minimize the risk of contamination during cell culture expansion?
- ◇ Does the firm adhere to application commitments for in-process parameters and controls for seed train and inoculum train propagation (e.g., as appropriate, seeding/cell density, agitation, temperature, pH, dissolved oxygen, cell culture duration, cell viability)?

E. Post-Expression Harvest and Recovery

- ◆ If the firm experienced process deviations related to harvest or clarification activities (e.g., filter clogging), did it handle the deviations appropriately, including assessing their impact on product quality?

Supplemental question:

- ◇ Does the firm conduct its harvest and clarification activities in accordance with BLA commitments?

F. Ultrafiltration/Diafiltration

- ◆ Does the firm have product-dedicated UF/DF membranes?
- ◆ Does the firm have protocols and reports, including interim reports, available for full-scale UF/DF membrane lifetime studies? Do lifetime studies support the performance of membranes throughout their lifetimes?
- ◆ If full-scale lifetime validation studies have been completed, are the membranes used in production within their validated lifetimes?
- ◆ Do bioburden, endotoxin, and other monitoring and testing results support adequate cleaning and storage of the membranes?
- ◆ Do the firm's UF/DF operation parameters (i.e., transmembrane pressure, diafiltration volume, pH, conductivity, yield) remain within acceptable ranges? If there are excursions, does the firm investigate those excursions and explain them in the relevant batch records or deviation reports?

Supplemental questions:

- ◇ Does the firm follow validated procedures for cleaning, sanitizing, and storing UF/DF membranes?
- ◇ Does the firm have data, such as water permeability results, to support cleaning effectiveness in removing product impurities? Do the water permeability criteria meet

vendor recommendations or other established criteria? Is testing conducted at an appropriate frequency?

- ◇ Are filters tested for integrity (air flow/pressure hold) at an appropriate frequency, and are results acceptable?

#### G. Column Chromatography

- ◆ Are the firm's column housings (the hardware containing the purification resins) clean and free of leaks, discoloration, and encrusted salts?
- ◆ Are the firm's resins product-dedicated?
- ◆ Are the ligand and matrix types used for column chromatography steps consistent with BLAs?
- ◆ Does the firm have protocols and reports, including interim reports, available for full-scale resin lifetime studies? Do lifetime studies support the performance of resins throughout their lifetimes?
- ◆ If full-scale lifetime validation studies have been completed, are the resins used in production within their validated lifetimes?
- ◆ Do bioburden, endotoxin, and other monitoring and testing results support adequate cleaning and storage of the chromatography columns?
- ◆ Are chromatography traces **consistent** from batch to batch (not necessarily identical)?
- ◆ Do chromatography column step yields indicate consistent manufacturing?
- ◆ If conductivity, back-pressure, or UV-absorbance excursions were encountered during recent column chromatography steps, did the firm investigate the excursions and explain them in the relevant batch records?

#### Supplemental questions:

- ◇ For columns with housings allowing a view of the resin bed, are the beds free from discolorations and pockets or streaks of air? Are column housing surfaces in direct contact with resin or product free from rust and corrosion? Does the top column frit contact the top of the media bed directly (without a gap)?
- ◇ Does the firm have protocols for packing and unpacking columns? Are the packing criteria consistent with the resin vendor's recommendations or other appropriate criteria? Do the firm's column packing data (e.g., asymmetry and height equivalent to theoretical plate data) demonstrate adequate column packing?
- ◇ Does the firm have and follow validated procedures for cleaning, sanitizing, and storing resins?

## H. Viral Clearance/Inactivation

### (1) Viral Filtration

- ◆ Are viral filtration steps performed as defined in relevant BLAs? Are parameters held within the ranges specified in the applications?
- ◆ Do viral filter post-use integrity testing results conform to established acceptance criteria?
- ◆ Does the firm monitor transmembrane pressure and flux rate for viral filtration steps? If the firm experiences excessive filter fouling (flux decay or pressure drop), does it appropriately investigate and implement appropriate CAPAs?

#### Supplemental question:

- ◇ Does the firm use the same viral filter brands and models as indicated in relevant BLAs? Does the firm use viral filters only once? If not, does the filter manufacturer recommend reuse and did the firm study reuse as a part of viral clearance studies?

### (2) Viral Clearance/Inactivation Processes

- ◆ Does the firm perform viral clearance/inactivation steps as defined in relevant BLAs? Are parameters held within the ranges specified in the applications?
- ◆ Are critical instruments used to measure viral clearance/inactivation conditions (e.g., flow meters, pH meters, conductivity meters) appropriately calibrated?
- ◆ If applicable, does the firm adequately investigate and document discrepancies related to viral clearance/inactivation (including filter integrity testing failures), performing appropriate CAPAs in a timely manner?
- ◆ If there have been recent changes to viral clearance processes (or equipment), did the firm evaluate the changes for their potential impact on product quality, and were they reviewed and approved by appropriate organizational units and submitted to FDA as appropriate?

## I. Bulk Drug Filtration and Fill

- ◆ Does the firm have records to demonstrate post-use integrity testing of bioburden reduction filters used during the final protein DS filling? Are adequate procedures in place for filter integrity testing and for determining a course of action if the integrity test fails?
- ◆ If applicable, does the firm adequately investigate and document filter integrity failures, performing appropriate CAPAs in a timely manner?
- ◆ Does the firm follow the vendor recommendation for use (e.g., filter pre-flush)? If not, has the firm conducted a risk assessment to determine that the vendor recommendation for use is not necessary?

- ◆ If the filling process is not closed, is the firm's bulk protein DS fill procedure adequate to prevent contamination and cross-contamination?
  - ◆ Is the open protein DS filling operation conducted under appropriate conditions for microbial control?
  - ◆ Are the operators adequately gowned?
  - ◆ Are the firm's changeover procedures for the bulk filling area and filling room adequate to prevent cross-contamination?
  - ◆ Do the firm's EM data meet acceptance criteria?
- ◆ If the firm's batch records contain prespecified criteria for bioburden reduction filter performance (e.g., flow rate, pressure), is performance appropriately monitored and does the firm meet the performance criteria?

Supplemental questions:

- ◇ Is the protein DS container closure system as indicated in the application?
- ◇ Is the protein DS filling operation conducted under conditions designed to maintain microbial control (e.g., biologic safety cabinet or ISO 5 type of environment)?

J. Bulk Storage of Protein DS

- ◆ Are significant storage excursions fully investigated?

Supplemental questions:

- ◇ Is the protein DS adequately labeled to prevent mix-ups?
- ◇ Is the protein DS stored in an area with controlled access and under appropriate conditions so that quality, purity, and strength are not affected?

5. **Laboratory Control System**

A. All Laboratory Disciplines

Supplemental question:

- ◇ Are the firm's laboratory analysts and management staff qualified to analyze, review, and evaluate data and quality assurance/quality control requirements?

(1) **Sampling**

- ◆ Does the firm have procedures for raw material sampling and testing? Is the firm's raw material sampling adequate to ensure proper conclusions on raw material disposition?

Supplemental questions:

- ◇ Is the firm's in-process material sampling consistent with sampling described in relevant BLAs? Is the firm's in-process sampling appropriate for monitoring the manufacturing process?
- ◇ Are the firm's sampling plans for protein DS release testing consistent with sampling plans defined in relevant BLAs and representative of the batch being tested?
- ◇ Does the firm have adequate sample tracking? Is an adequate system in place to ensure that samples are stored appropriately and that the correct samples are tested within appropriate time frames specified in SOPs?
- ◇ Does the firm store test samples under conditions that prevent stress or destruction? Are microbial bioburden and endotoxin samples stored at 2–8°C for less than 24 hours? If other storage conditions are used for bioburden and endotoxin samples, are data available to demonstrate that recovery/viability is not compromised by the storage conditions?

**(2) Test Methods**

- ◆ Are the firm's test methods consistent with those described in relevant BLAs? Do the acceptance criteria match those described in relevant applications?

Supplemental question:

- ◇ Does the firm have adequate SOPs for each assay? Do assays have adequate system suitability criteria?

**(3) Record Keeping**

- ◆ Do the firm's laboratory raw data match those that are formally recorded into a laboratory information management system (LIMS) or other computer data storage systems?

Supplemental questions:

- ◇ Does the firm have appropriate procedures for handling test data, including raw data?
- ◇ Does the firm have complete test records, including raw data, calculations, and comparisons to established acceptance criteria?
- ◇ Does the firm correctly apply statistical methods, including averaging, if appropriate?
- ◇ Does the firm record adequate information for investigational purposes when conducting each assay? (This may include, for example, lot numbers of reagents and standards, equipment calibration statuses, system suitability results, and step-by-step check-off procedures.)
- ◇ Does the firm adequately record departures from assay protocols?



#### (4) Laboratory Equipment, Reagents, and Standards

- ◆ Based on a review of select laboratory equipment qualification reports, does the firm appropriately qualify laboratory equipment?
- ◆ Are the firm's reagents and chemicals within expiry and stored appropriately?

##### Supplemental questions:

- ◇ Does the firm have appropriate programs and procedures for the preventive maintenance and calibration of laboratory equipment? Are equipment calibrations and preventative maintenance within expiry? (See also Part III.4.A(3)—[Equipment Maintenance and Calibration](#).)
- ◇ Are the firm's stability chamber temperature and humidity chart readers appropriately maintained and operating in a state of control?
- ◇ Does the firm use appropriate chemical or biological standards for equipment calibration and test method validation?

#### (5) Test Method Validation and Postapproval Changes

- ◆ For recently added test methods, were the new methods appropriately reported and do the firm's raw data support its validation conclusions?
- ◆ If there have been recent changes to validated test methods, did the firm evaluate the changes for their potential impact on product quality, and were they reviewed and approved by appropriate organizational units? Does the firm have data demonstrating that the changes do not negatively impact the performance of the assays? Were changes appropriately reported? If warranted, did the firm handle the modifications appropriately in terms of validation?
- ◆ If the firm has had test methods transferred to its laboratory, do method transfer reports confirm that the transferred methods perform consistently among laboratories?

##### Supplemental question:

- ◇ If the firm encountered problems with assay performance postapproval, did it take appropriate steps to address the issues?

#### (6) Out-of-Specification Results and Invalid Tests

- ◆ For products or in-process tests originally yielding an OOS result, did the firm justify repeated tests by adequately invalidating the original test result? If not, does the firm have an acceptable justification for the repeated testing?
- ◆ If material does not meet release or stability acceptance criteria (or exceeded action limits), does the firm appropriately investigate and handle material disposition?

- ◆ Does the firm evaluate repeatedly invalid tests? Does the firm take appropriate and timely actions in response to identified issues? Does the firm's management demonstrate adequate oversight of analysts and assays in instances of repeatedly invalid tests?

Supplemental question:

- ◇ Does the firm have and follow SOPs for investigating OOS test results? Do these SOPs conform to appropriate guidance, such as guidance for industry *Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production*, if applicable? If not, are the differences justifiable? Does the firm's OOS SOP prohibit retesting into compliance, and are all results appropriately reported?

### **(7) Stability Testing and Reserve Samples**

- ◆ Does the firm conduct stability studies using the appropriate container (i.e., representative of the manufacturing container) and appropriate storage conditions as described in the approved BLA, supported by data or records associated with stability chamber monitoring?

Supplemental questions:

- ◇ Are the firm's raw stability data accessible, and do the raw data support reported results?
- ◇ Are the firm's reserve samples stored in the same packaging system as the bulk protein DS, stored at the same recommended temperatures, and retained for an appropriate period post-expiry?
- ◇ Are the firm's expiry or retest dates the same as indicated in the relevant applications?

## **B. Biotechnology-Specific Testing**

### **(1) Potency Assays/Bioassays**

- ◆ For protein biological products for which the firm conducts potency testing on-site, are the potency assays conducted as described in relevant BLAs?

Supplemental question:

- ◇ Does the firm conduct its potency testing with appropriate controls in place?

### **(2) Protein Reference Standards**

- ◆ Are the product reference standards used by the firm the same as those listed in relevant BLAs?
- ◆ For new reference standards in use since the last inspection, were they qualified using an FDA-approved protocol or was the change reported in a supplement?

- ◆ Does the firm have reference standard requalification protocols to ensure that reference standards remain suitable for use over time? Does the firm follow all reference standard requalification protocols from BLAs?
- ◆ Are procedures for the storage and tracking of the reference standards adequate?

### C. Microbiological Testing

#### (1) Bacterial Endotoxin Testing

- ◆ Does the firm have and follow written and approved procedures for the periodic evaluation of endotoxin testing results, and does it respond appropriately to adverse trends?

#### Supplemental questions:

- ◇ Does the firm conduct endotoxin testing for in-process material and bulk protein DS samples in strict accordance with the methods in the approved BLA and with its SOPs? Are test samples representative?
- ◇ If the firm uses USP General Chapter <85> *Bacterial Endotoxins Test*, which describes the limulus amebocyte lysate techniques for the detection of bacterial endotoxin:
  - Are the tests supported by product-specific suitability studies (inhibition/enhancement studies)?
  - If the firm employs the gel-clot method for limulus amebocyte lysate testing, do they locate the heating block in an area of the laboratory free of vibration?
  - If a protein DS requires dilution to overcome product interference, has the firm appropriately calculated the maximum valid dilution? Do test records indicate that the firm does not dilute beyond this calculation?
- ◇ If conducting OOS investigations for bacterial endotoxin results, does the firm review the manufacturing process for possible gram-negative microorganism contamination routes (e.g., water system, columns, UF/DF systems)?
- ◇ To aid its investigation into the potential source of endotoxin and to assess product impact, does the firm determine the level of bacterial endotoxin in the protein DS if an endotoxin test result is OOS (rather than simply using the product dilution to determine whether the DS is within specification)?

#### (2) Bioburden and Mycoplasma Testing

- ◆ Does the firm conduct appropriate controlled growth promotion testing on each lot of testing media used?
- ◆ Does the firm have and follow written and approved procedures for the periodic evaluation of bioburden testing results, and does it respond appropriately to adverse trends? Does the firm

appropriately test for the presence of mycoplasma according to validated protocols described in the approved BLA?

Supplemental questions:

- ◇ If specific concerns exist for certain raw materials, does the firm's microbial testing provide assurance that fastidious microorganisms indigenous to those materials (e.g., mycoplasma, anaerobic bacteria, fungi) will be recovered with the test media under the test conditions?
- ◇ Are the firm's bioburden limits and action levels consistent with those set in relevant BLAs?
- ◇ If the firm obtains an OOS or an action level value for a bioburden limits test result, does the firm's laboratory perform microbial identification on all isolates? Are the identified OOS or action level microorganisms compared to isolates recovered from raw material, EM, or water testing results?
- ◇ If USP General Chapter <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* is referenced/employed by the firm, is it conducted as qualified? (See specifically the method suitability discussion in General Chapter <61>.)

### (3) Identification of Microorganisms

- ◆ Does the firm conduct microbial identification on (1) isolates recovered from action level EM excursions, and (2) organisms found in the product if the microbial counts exceed action levels? If not, is the firm's justification for not doing so adequate?

Supplemental questions:

- ◇ Has the firm appropriately validated/qualified the microbial identification platforms it uses according to either the manufacturer validation protocol described in the BLA or a recognized procedure, such as that described in USP General Chapter <1113> *Microbial Characterization, Identification, and Strain Typing*? If not, is the firm's validation/qualification acceptable (based on a detailed review)?
- ◇ Does the laboratory appropriately store physical isolates requiring identification? Do the firm's original isolates, held on agar plates or slants, have a record of their existence within LIMS? (The isolates are usually labeled with the sample tracking number, product batch number, EM location, and so forth.)

### (4) Viral Safety Testing

- ◆ Are raw materials of human or animal origin tested for viral contamination in accordance with application requirements? For materials tested by the material vendor, has the firm appropriately qualified the vendor? Based on the inspection team's review of raw material COAs (for a set period of time), do the materials meet application requirements?

- ◆ Is testing at the end of mammalian cell culture (e.g., unprocessed bulk) being conducted per application requirements? Have the firm's unprocessed bulk samples all tested negative for adventitious viruses?
- ◆ Does the firm ensure the testing of all cell banks per application requirements (almost always as described in ICH guidance for industry *Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*)? Do test reports confirm that each assay listed in the relevant BLA (e.g., in vitro, in vivo, virus-specific) has been performed and that all results are acceptable? (There will generally be a table in the application that lists each test for each cell bank.)

#### D. Contract Testing Laboratories

- ◆ If applicable, has the firm appropriately qualified off-site testing laboratories to conduct in-process, release, or other testing (e.g., raw materials testing)? Does the firm have quality agreements or other appropriate agreements with the contract testing laboratories detailing responsibilities such as reporting deviations, reviewing and reporting OOS results, reviewing raw data, and validating test methods?
- ◆ Does the contract laboratory conduct required suitability tests to ensure noninterference by products tested using either the validated in-house method or the compendial tests, including bacterial endotoxin and bioburden tests?

#### Supplemental question:

- ◇ Does the firm receive reports/results (including initial and confirmed OOS results) signed by the testing laboratory's quality assurance department, and can the firm obtain raw data upon request? Does the firm have experienced personnel who review and assess these reports/results?

### 6. Packaging and Labeling System

- ◆ Are protein DS shipped in accordance with validated and documented shipping procedures?
- ◆ If the firm uses a contract shipper (third party), does the firm have a documented process to qualify the contract shipper's capability to adhere to the specific shipping conditions and procedures needed to transport protein DS?
- ◆ Are qualified containers, methods, and shippers used?

#### Supplemental questions:

- ◇ Are protein DS containers appropriately labeled, ensuring the correct batch number, particularly for batches filled into several containers?
- ◇ Does the firm have and use procedures to confirm that labels contain the correct information and conform to specifications in the master batch record? Does the firm have

and use procedures to reconcile differences between the numbers of labels issued and used?

- ◇ Are containers holding different batches of protein DS appropriately segregated to avoid potential mix-up?
- ◇ If the firm has encountered protein DS container leakage, have the leakage events been appropriately investigated, with proper action taken? Does the firm have well-justified disposition decisions for containers holding potentially affected protein DS?
- ◇ Does the firm appropriately limit access to final bulk protein DS?
- ◇ Does the firm have a written procedure regarding packing for shipping, specifically addressing temperature requirements?
- ◇ Do shipping data confirm that protein DS are maintained at the appropriate temperature throughout the shipping process?

## ATTACHMENT B: HIGHLY POTENT OR TOXIC PRODUCTS

Firms using multiproduct facilities to manufacture highly potent or toxic products should (1) use appropriate risk management tools to assess cross-contamination risks, and (2) implement control strategies to mitigate cross-contamination and mix-up risks to acceptable levels. Specifically, firms are expected to have a quality risk management plan for cross-contamination. The firm should use facility design, segregation, and process and procedural controls to control cross-contamination risks involving highly potent or toxic products.

This attachment is only applicable to the manufacture of highly potent or toxic products in a **multiproduct** facility that does not provide product-dedicated buildings for highly potent and toxic product operations.

References:

- International Council for Harmonisation (ICH) guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, section IV.D, Containment
- International Society for Pharmaceutical Engineering (ISPE) *Baseline Guide Volume 7 Risk-Based Manufacture of Pharmaceutical Products* (2010)
- ◆ Does the firm periodically review its risk management report for highly potent or toxic product cross-contamination to ensure that cross-contamination risks are continuously at an acceptable level?

The questions below should be reviewed together with the firm's quality risk management plan to ensure that cross-contamination risks are reduced to an acceptable level.

### 1. Process Containment

- ◆ Do data, such as pressure hold test data and glove integrity data, indicate that the firm adequately maintains the integrity of the environment (e.g., isolator) used to contain the weighing and dissolving of highly potent compounds (e.g., cytotoxic drug compounds used to produce antibody-drug conjugates)?
- ◆ Do pressure differential data indicate that the firm maintains an adequate pressure differential between highly potent or toxic product manufacturing areas and surrounding areas and that it effectively uses airlocks to contain the process and protect products?
- ◆ Does the firm's flow of equipment, products, raw materials, and waste adequately prevent cross-contamination through product crossover points?
- ◆ Do the firm's gowning and personnel flow adequately prevent cross-contamination of other areas with highly potent or toxic compounds?
- ◆ Does the firm have adequate procedural controls for preventing mix-ups such as the accidental use of highly potent or toxic compounds or equipment contaminated with those compounds?

- ◆ If applicable, does the firm follow its spill control procedures following spill incidents?

## 2. Cleaning and Changeover

For each highly potent or toxic product manufactured, the firm should establish, based on toxicological data, the acceptable daily exposure (ADE): “a dose that is unlikely to cause an adverse effect if an individual is exposed, by any route (e.g., intrathecal, inhaled) at or below this dose every day for a lifetime,” as defined in ISPE Baseline Guide Volume 7. This value should be used to calculate the acceptance criteria for highly potent product residue for cleaning validation and verification.

- ◆ Is cleaning verification conducted after cleaning shared product-contact equipment during each changeover?<sup>33</sup>
- ◆ Do data for cleaning verification and requalification (if appropriate) for shared product-contact equipment meet the predetermined product carryover limits established using toxicologically derived ADEs?
- ◆ If the firm has been unable to achieve its predetermined product carryover limit for the cleaning of a highly potent or toxic product, has the firm switched to dedicated or disposable equipment and reported to FDA, as appropriate?
- ◆ Does the firm remove dedicated equipment, raw materials, ancillary room items, and waste from shared areas? If equipment removal is not feasible, does the firm decontaminate and clean the equipment using validated procedures?
- ◆ After cleaning, does the firm release highly potent or toxic product shared areas in accordance with quality unit-approved procedures?
- ◆ Is cleaning verification conducted for the surfaces in any shared areas used to weigh and dissolve highly potent compounds? Do data for cleaning verification and requalification (if appropriate) meet the predetermined acceptance criteria for highly potent residues established using toxicologically derived ADEs?

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<sup>33</sup> This is an expectation in the vast majority of cases; however, it is not an absolute requirement. With appropriate justification, based on a thorough risk analysis, the firm may choose not to practice cleaning verification for each changeover if cleaning validation has been completed.



## ATTACHMENT C: SPORE-FORMING MICROORGANISMS

Firms should make special considerations if manufacturing drug substance using spore-forming microorganisms. If spore-forming microorganisms are employed for manufacture at multiproduct facilities, firms may either use a dedicated building for these operations or practice product containment. If a dedicated building is not used, the inspection team should evaluate whether the firm has and effectively uses appropriate containment practices. This includes demonstrating that spore-forming microorganisms are effectively removed from the facility and equipment before introducing other products, ensuring that personnel flow does not allow for inadvertent contamination, and conducting environmental monitoring (EM) for spore-forming microorganisms in appropriate areas.

For biologics license applications, regulations for working with spore-forming microorganisms are found at 21 CFR 600.10(b)(3) and 600.11(e)(3).

### References:

- International Council for Harmonisation (ICH) guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, section IV.D, Containment
- Guidance for industry *Manufacturing Biological Intermediates and Biological Drug Substances Using Spore-Forming Microorganisms* (September 2007)

### 1. Process Containment

- ◆ Does the firm conduct manufacturing processes/steps with spore-forming microorganisms in an isolator or in areas with negative air pressure (relative to the surrounding areas)? Has the firm adequately designed personnel and material airlocks for spore containment (e.g., pressure sinks)? Does the firm monitor the pressure differential?
- ◆ Does the firm have appropriate air handling units in areas where spore-forming microorganisms are used? Is the exhaust air filtered through high-efficiency particulate air filters?
- ◆ Are the firm's gowning and personnel flow adequate to prevent the spread of spores to other areas?
- ◆ Are materials, equipment, and waste decontaminated before being removed from manufacturing areas where spore-forming microorganisms were used? Has the firm validated the effectiveness of its spore decontamination procedures? Does the firm conduct EM for spore-forming microorganisms in areas adjacent to production areas where spore-forming microorganisms are used? Has the firm qualified the EM test method used to detect spore-forming microorganisms for specificity, sample recovery, and detection limits?
- ◆ Are procedures in place for containing spills and decontaminating and cleaning areas and equipment affected by spills?

## 2. Changeover

- ◆ Does the firm decontaminate and remove dedicated equipment, raw materials, ancillary items, and waste from shared areas? If equipment removal is not feasible, does the firm decontaminate, clean, and sterilize (if applicable) equipment with validated procedures?
- ◆ Does the firm decontaminate or sterilize shared equipment during changeover?
- ◆ Have the changeover processes been validated?
- ◆ Does the firm monitor for residual spore formers after decontaminating and cleaning with adequate sampling locations and methods? Has the firm qualified the test method used to detect spore-forming microorganisms for specificity, sample recovery, and detection limits? (If the firm sterilizes the equipment, residual spore formers need not be monitored.)
- ◆ Does the firm have and use adequate procedures for decontaminating areas where spore-forming microorganisms have been used before introducing subsequent products to manufacturing areas? Has the effectiveness of these procedures been validated?
- ◆ Is the area cleaned and released for use in accordance with quality unit-approved procedures? Do EM data for the spore-forming microorganism demonstrate removal of the microorganism from the shared area?