Compliance Program Guidance Manual
Chapter – 45 Biological Drug Products
Inspection of Biological Drug Products (CBER)
7345.848

Implementation Date: *January 1, 2010* **Completion Date:** *December 31, 2010*

Product Codes:		Programs/Assignment Codes:
*57A	Antitoxins (e.g., Botulism Antitoxin)/Antivenins (e.g., snake, spider)	45848A Pre-License Inspection -Allergenics
*57B	Immunization Toxoids (e.g., Diphtheria Toxoid, Tetanus Toxoid)	45848F Level 1 CGMP Inspection - Allergenics
*57C	Viral Vaccines (e.g., Rabies, Yellow Fever, Small Pox, Influenza Vaccines)	45848G Level 2 CGMP Inspection- Allergenics
*57E	In-Vivo Diagnostic Products (e.g., Tuberculin PPD (skin test))	45848B Pre-License Inspection -Vaccines
*57G	Allergenic Products (e.g., Allergenic Extracts, animal allergens, venoms)	45848C Level 1 CGMP Inspection -Vaccines
*57H	Bacterial Vaccines/Antigens (e.g., Pneumococcal Vaccine, Meningococcal Polysaccharide Vaccine)	45848D Level 2 CGMP Inspection –Vaccines
*57I	Multiple Vaccine/Multiple Antigen Preparations (e.g., Measles, Mumps, Rubella Vaccine; Diphtheria, Tetanus, and Pertussis Vaccine)	*45848 Off Year Flu PAC*
*57N	Human Cell and Gene Therapies (e.g., Cell Therapies, Vectors, Genetically Modified Cells	42848A Pre-License Inspection - Plasma Derivatives
*57U	Blood Derivatives (e.g., Albumin, Immune Globulin)*	42848F Level 1 CGMP Inspection - Plasma Derivatives
*57Y	Biological In-Vivo and In-Vitro Diagnostic Products Not Elsewhere Classified (N.E.C.)*	42848G Level 2 CGMP Inspection - Plasma Derivatives
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		41848A Pre-License Inspection - Therapeutic Drugs
		41848F Level 1 CGMP Inspection - Therapeutic Drugs
		41848G Level 2 CGMP Inspection - Therapeutic Drugs
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FIELD REPORTING REQUIREMENTS

Send Establishment Inspection Reports (EIRs) that contain issues requiring policy development or clarification to the Center for Biologics Evaluation and Research (CBER) for review. Send the EIR and relevant exhibits (**electronically, if possible**), to *cberinspections@fda.hhs.gov*, or by mail to:

Division of Inspections & Surveillance, HFM-650
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

Domestic Inspections:

Inspections classified NAI and VAI: *Notify* CBER, Office of Compliance and Biologics Quality (OCBQ), Division of Inspections and Surveillance (DIS) HFM-650 *at cberinspections@fda.hhs.gov, when EIRs are available in Turbo EIR.* Do not submit exhibits unless specifically requested. Send an electronic copy of the EIR narrative to Office of Regional Operations (ORO) HFC-100.

Inspections classified OAI: Send a complete copy of the EIR, including exhibits, and the FACTS coversheet with endorsement and classification to OCBQ/DIS/HFM-650 and HFC-100.

Regardless of classification, send the complete original report, with exhibits, to the home district.

Foreign Inspections:

CBER acts as the "home district" for foreign inspections of CBER-regulated products. Send the complete original EIR, with exhibits, to OCBQ/DIS/HFM-650, regardless of recommended classification. Send *an electronic* copy of the EIR narrative, and FACTS coversheet with endorsement to HFC-100.

Inspection Reporting – Endorsement Section of EIR

The FACTS endorsement (Inspection Summary field) shall include the following information in addition to the information specified in the Investigations Operations Manual (IOM).

1. *The inspection level.*
2. For a Level II inspection, list the systems inspected.
3. Note when an expected Level II inspection is changed to Level I based on *findings* of significant objectionable conditions during the inspection.

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PART I - BACKGROUND

CBER-regulated biological drug products include fractionated blood and their recombinant analogues; antitoxins; allergenic products; vaccines; products that of manipulated, cultured or expanded human cells, and gene *therapy* products that introduce genetic material into the body to replace faulty or missing genetic material.

CBER is responsible for ensuring biological drug products are safe and effective, and are in compliance with FDA and other applicable laws and regulations. Biological drug products are licensed under Section 351 of the Public Health Service (PHS) Act (42 U.S.C), and fall within the definition of a drug, found in Section 201(g)(1) of the Food, Drug, and Cosmetic Act (FD&C Act), and are inspected under the provisions of both the PHS Act and the FD&C Act.

Biological drug products are subject to the applicable regulations promulgated under both Acts, including the Current Good Manufacturing Practice regulations (CGMPs), which are found in Title 21 Code of Federal Regulations (CFR), Parts 210 and 211, and the Biologics regulations, 21 CFR Parts 600-680. Section 501(a)(2)(B) of the FD&C Act requires that biological drug products be manufactured in compliance with CGMPs. CGMP regulations apply to the manufacture of biological drug products and CGMP principles apply for the manufacture of biological intermediates and drug substances under Section 501(a)(2)(b) of the FD&C Act, and the Biologics regulations under 21 CFR Part 600.

Establishments must also comply with their biologics license application (BLA) commitments, and applicable standards. Biological drug products include a wide variety of indications, dosage forms and manufacturing processes, all of critical importance to promoting and protecting the public health. To help ensure the industry produces these important biological drugs to be consistently safe, pure, potent, and effective, FDA conducts CGMP inspections of each establishment at least biennially.

To provide more effective and efficient regulation of biological drug products, the Office of Regulatory Affairs (ORA) and CBER established Team Biologics in 1997 to conduct routine and compliance follow up CGMP inspections of biological drug product manufacturers, including blood establishments. Team Biologics uses the investigative skills of ORA and the medical/scientific and product expertise of CBER, to promote and protect the public health through coordinated, integrated assessments of the compliance status of biological drug manufacturers.

This compliance program builds upon the knowledge gained during previous FDA inspections of the biological drug industry. It reflects the objectives identified in FDA's Strategic Action Plan for developing and implementing new inspection approaches using a resource efficient, risk-based approach to provide high quality, cost-effective oversight of industry manufacturing, processing, and distribution of biological drug products to reduce risk.

This risk-based management approach identified six key systems and three critical elements within each system that are common to establishments making biological drug products. Most products covered under this compliance program were identified as critical to public health (e.g., sole source, important medical need; childhood vaccines, etc.), and most products are aseptically processed. These factors help form the basis for establishing appropriate levels of inspection coverage under this risk-based program.

This program also establishes two levels of inspectional coverage to evaluate an establishment's compliance with applicable CGMP regulations; Level I – includes all six systems in a comprehensive evaluation, and Level II – includes two mandatory systems, plus one additional system on a rotating basis in a streamlined evaluation. This approach is similar in concept to that set forth in CBER's CPG 7342.001- Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors, that incorporates a systems-based approach with critical elements to be covered within each system, and a Level I/II inspection option.

This risk-based quality management approach focuses on the key operating systems within the facilities and the two-tiered inspection option provides a method to focus the inspectional coverage and resources appropriate for each inspection, and to implement the appropriate advisory, administrative, or regulatory action, when necessary.

Continued biennial inspections under this compliance program will:

- Safeguard the public health by reducing the risk of adulterated or misbranded biological drug products reaching the marketplace;
- Increase communication between the industry and the Agency, and
- Provide timely feedback during inspections to improve their compliance with CGMP's.

Subsequent to implementation, CBER will evaluate its experience with this systems-based program to determine its effectiveness, and to assess and improve the quality of the CBER products inspections program.

PART II- IMPLEMENTATION

A. OBJECTIVE

This compliance program combines and replaces the compliance programs for licensed allergenics (7345.001), licensed vaccines (7345.002), plasma derivatives (7342.006) and therapeutic drugs (7341.001). This program represents a continuing compliance and surveillance activity conducted to ensure that CBER-regulated biological drug products for human use are safe, pure, potent, effective, and appropriately labeled. The inspection of a facility is performed to ensure that manufacturers are making products that:

- Meet the standards described in applicable provisions of the regulations. These include regulations in 21 CFR Parts 600, 601, 610, 640, 660, 680, and 1271, CGMP regulations in 21 CFR Part 200, 201, 210 and 211.
- Meet any additional conditions of licensure in the approved Biologics License Application (BLA) and/or supplements, if manufacturing a licensed product, and other applicable standards.

This compliance program provides inspectional guidance to investigators assigned to perform biennial or for cause inspections of manufacturers of CBER-regulated biological drug products, and provides administrative/regulatory guidance for the compliance officer (CO) or investigator (hereinafter referred to as "investigators"). It includes information regarding noncompliance with applicable regulations, provides information necessary to evaluate overall operations, including quality assurance and quality control programs of the inspected facilities, and ensures that appropriate enforcement actions are initiated against those manufacturers found to be in significant noncompliance with applicable laws and regulations.

Firms covered under this compliance program include the following: all licensed manufacturers of vaccines and related products, including source material manufacturers and licensed bulk manufacturers; all licensed manufacturers of allergenic products (allergenic patch test manufacturers are not included); unlicensed source material suppliers; all licensed manufacturers of fractionated products, certain recombinant products, and certain human cell, tissue, and cellular and tissue-based products (HCT/Ps) regulated as drugs, and/or biological products. (Note that these products are also subject to good manufacturing practice (GMPs) contained in parts 210 and 211.)

B. STRATEGY

This compliance program incorporates a systems-based, risk management approach to conducting inspections, and identifies six key systems and three critical elements within each system for inspection.

The six key systems are:

1. Quality System
2. Facilities and Equipment System
3. Materials System
4. Production System
5. Packaging and Labeling System
6. Laboratory Control System

The three critical elements are:
1. Standard Operating Procedures (SOPs)
2. Training
3. Records

The inspection of biological drug manufacturers is conducted under either a Level I or Level II inspection option. This compliance program directs an in-depth audit of the critical areas in each system, which may affect the safety, purity, potency, identity, and effectiveness of the biological drug, if procedures are not performed properly or the system controls are either inadequate or not functioning correctly.

- A Level I inspection is an in-depth audit of the three critical elements in each of the six systems, and provides a comprehensive evaluation of the establishment's compliance with CGMPs.
- A Level II inspection is a streamlined evaluation of an establishment's compliance with CGMPs, and provides coverage of the three critical elements in two mandatory systems (Quality Systems and Production System), plus at least one additional system on a rotating basis during successive biennial inspections.

See Part III, Inspections, for selection criteria for Level I and Level II inspections.

C. PROGRAM MANAGEMENT INSTRUCTIONS

1. Precautionary Measures

Due to the nature of the materials used to manufacture certain biological drug products, investigators may be required to provide proof of inoculation against a particular disease agent or undergo certain medical evaluations prior to beginning an inspection. Investigators should be aware of any such requirements and ensure they are met in sufficient time prior to the start of the inspection, so as to make certain the inspection schedule will not be disrupted.

Additionally, in many cases, the active materials used to manufacture biological drug products are hazardous to the health in their initial form. For this reason, investigators must exercise extreme care when performing inspections of manufacturing areas, to ensure they do not come into direct contact with these materials.

2. Frequency of CGMP Inspections

CGMP inspections are statutory obligations that are routinely conducted on a biennial schedule; however, inspections may be conducted more often if circumstances, such as the firm's compliance history, so warrant.

Exceptions:

This inspectional frequency does not apply to firms that meet the following conditions; additionally, these firms must be inspected using the Level I Inspection Option.

- Firms under a Consent Decree of Permanent Injunction, which have varied inspection schedules set by either the consent decree and/or a consent decree working committee

- Firms under Notice of Intent to Revoke and/or other administrative actions
- Compliance follow-up inspections to verify a firm's implementation of corrective action after a regulatory action has been taken
- A newly licensed or registered facility

3. Scheduling of Inspections and Assignment of Investigators

Under Team Biologics, the Team Biologics (TB) *Supervisory Investigator* (or designee) works with CBER/OCBQ/DIS to develop the workplan schedule of inspections, and to ensure CBER product specialist participation, either on-site or by consult, in CGMP inspections. All parties attempt to minimize rescheduling of inspections, but changes are at times necessary. The TB *Supervisory Investigator* promptly notifies and consults with CBER regarding schedule changes.

After reviewing the establishment's inspectional history and other relevant information, biological drug product manufacturers will be scheduled for either a Level I or Level II inspection.

The inspections will be conducted using a team approach with a Team Biologics Core Team investigator leading, and a CBER product specialist participating. The inspection team may include other ORA or CBER members, as necessary, to ensure appropriate coverage of the facility being inspected. If CBER on-site participation is not possible, the Core Team member(s) alone will conduct the inspection, with participation of product specialist off-site (e.g., telephone).

Other inspections:

CBER is responsible for the conduct of all pre-license (PLI) and pre-approval (PAI) inspections of CBER-regulated products. These inspections are part of the review of a BLA or supplement. CBER identifies the scope and content of the inspection and invites ORA to participate in the inspections. CBER/OCBQ, Division of Manufacturing and Product Quality (DMPQ) will notify the district office and the TB *Supervisory Investigator* of all pending pre-license or pre-approval inspections.

PART III - INSPECTIONAL

A. INSPECTIONAL PROCEDURES

Review and use the applicable sections of Chapter 5 of the Investigations Operations Manual (IOM); Compliance Program 7356.002, Drug Manufacturing Inspections; 7356.002A, Sterile Drug Process Inspections; guidance applicable to the manufacture of CBER regulated drug products, and other pertinent documents provided by CBER. If there are differences between the above referenced documents and the instructions in this program, investigators should follow the instructions in this program when conducting inspections.

Source material suppliers are subject to the requirements in 21 CFR Parts 600-680. Because they are not finished product manufacturers, the drug CGMP regulations in Parts 210 and 211 may not be directly applicable. However, they are required to comply with CGMPs in the context of section 501(a)(2)(B) of the Act, to ensure the products have the quality, purity, and identity they purport. If there are questions regarding the appropriateness of one or more particular inspectional observations; relating to a source material supplier, such as suppliers of animal source materials for animal derived products, e.g., antitoxin and porcine Factor VIII; the Team Biologics CO should review the observation(s) before inclusion on the Form FDA 483, Inspectional Observations.

If it is necessary to verify the content of a license application or supplement or if there is an apparent conflict between the approved license and any FDA guidance documents or regulations, contact CBER/OCBQ/DIS, and the relevant product office for assistance.

The Team Biologics Core Team, including the appropriate product specialist, in conjunction with CBER/OCBQ/DIS and the home district, will develop the overall inspectional approach for individual CGMP inspections. Products needing special coverage will be addressed as part of the specific inspectional approach.

B. SYSTEMS DEFINITION

Inspections of biological drug product manufacturers are to be conducted and reported using the systems and organization defined in this compliance program. In addition to the areas of inspectional focus described below for each system, system assessment should include a walk-through of the facilities whenever possible.

1. Quality System

This system assures overall compliance with CGMPs, internal procedures, and adherence to specifications. It includes, but is not limited to the following: the quality control unit (QC) and all of its review and approval duties; such as release of components and in-process materials, change control, reprocessing, batch release, annual record review, validation protocols and reports; all BPD evaluations; complaint handling, and evaluation of returned and salvaged products, including evidence of counterfeit products.

Assessment of the Quality System is two-phased. The first phase is to evaluate whether the QC unit has fulfilled its responsibility to review and approve all procedures related to production, quality control and quality assurance, and to ensure the procedures are adequate for their intended use. This also includes the associated record keeping systems.

Review records related to product recall, product deviations, complaints, out of specification results, rejects, and failure investigations. Verify the firm routinely reviews its records pertinent to the manufacture of lots or units prior to their release or distribution. Examine, report, and track counterfeit imported products, returned and rejected imported products, and complaint files concerning imported products. The second phase is to assess the data collected in order to identify quality problems that may be linked to other systems.

2. Facilities and Equipment System

This system includes the measures and activities that provide an appropriate physical environment, along with the equipment and resources that are used in the production of the biological drug product.

Coverage of this system should include verifying the appropriateness of buildings and facilities, including maintenance; equipment qualifications (installation and operation); equipment calibration and preventative maintenance; cleaning and validation of cleaning processes as appropriate, and utilities that are not intended to be incorporated into the product; such as HVAC, compressed gases, and steam and water systems. Process performance should be evaluated as part of the inspection of the overall process, which is done within the system where the process is employed.

3. Materials System

This system includes the measures and activities to control finished products, such as components, source materials, water or gases that are incorporated into the product, and containers and closures. The audit of this system should include examining the validation of computerized inventory control processes, product storage, distribution controls, records, and detection and prevention of counterfeiting, including counterfeit imported materials. Facilities used in support of this system must be maintained in a clean and orderly manner, and must be of suitable size, construction and location to facilitate adequate cleaning, maintenance and proper operation. The audit of this system should include a determination of significant physical changes, and an evaluation of routine monitoring of the utility systems. Equipment used in support of this system must be maintained in a clean and orderly manner, and located so as to facilitate proper cleaning and maintenance. The audit of this system should include review of procedures and records of calibration and maintenance, verification that the firm is following procedures and that the procedures conform to the manufacturer's recommendations and/or user manuals, and determination of any new equipment added, or if any modifications to existing equipment were made since the last inspection.

4. Production System

This system includes the measures and activities to control the manufacture of biological drug products, including following and documenting performance of approved manufacturing procedures. Inspection of this system should include, among other things, covering batch formulation; dosage form production; sterile filtration; aseptic filling; in-process testing; lot release, and process validation.

Review a sampling of records for operations performed. Verify that records are complete and maintained as required, and are related to the history and disposition of all products produced and distributed. All records must be legible and indelible, and must identify the person

performing the work, including dates of the various entries; show test results as well as the interpretation of results; show the expiration date assigned to specific products; and be as detailed as necessary to provide a complete history of the work performed.

Facilities used in support of this system must be maintained in a clean and orderly manner, and must be of suitable size, construction and location to facilitate adequate cleaning, maintenance and proper operation. The audit of this system should include a determination of significant physical and/or manufacturing changes, and an evaluation of routine monitoring of the utility systems. Equipment used in support of this system must be maintained in a clean and orderly manner, and located so as to facilitate proper cleaning and maintenance. The audit of this system should include review of procedures and records of calibration and maintenance, verification that the firm is following procedures and that the procedures conform to the manufacturer's recommendations and/or user manuals, and determination of any new equipment added, or if any modifications to existing equipment were made since the last inspection.

5. Packaging and Labeling System

This system encompasses the measures and activities that control packaging and labeling of biological drug products. Inspectional coverage should include review of the firm's written procedures regarding packaging and labeling controls. The firm's examination of labels and usage, and label storage and issuance should also be observed during the inspection. Facilities used in support of this system must be maintained in a clean and orderly manner, and must be of suitable size, construction and location to facilitate adequate cleaning, maintenance and proper operation. The audit of this system should include a determination of significant physical and/or manufacturing changes, and an evaluation of routine monitoring of the utility systems. Equipment used in support of this system must be maintained in a clean and orderly manner, and located so as to facilitate proper cleaning and maintenance. The audit of this system should include review of procedures and records of calibration and maintenance, verification that the firm is following procedures and that the procedures conform to the manufacturer's recommendations and/or user manuals, and determination of any new equipment added, or if any modifications to existing equipment were made since the last inspection.

6. Laboratory Control System

This system includes all the various measures and activities that are related to laboratory procedures; analytical methods development; validation or verification; and the stability program. An in-depth audit of this system should include review of the firm's SOPs for control of microbiological contamination and environmental monitoring; review of records for source materials, in-process and finished product testing; evaluation of the firm's methods for sampling and testing products for identity, potency, safety, sterility and conformance with final specifications; and review of the firm's test methods to ensure that they have been appropriately validated.

Review a sampling of records for operations performed verify that records are complete and maintained as required, and are related to the history and disposition of all products produced and distributed. All records must be legible and indelible, and must identify the person performing the work, including dates of the various entries.

Facilities used in support of this system must be maintained in a clean and orderly manner, and must be of suitable size, construction and location to facilitate adequate cleaning, maintenance

and proper operation. The audit of this system should include a determination of significant physical and/or manufacturing changes, and an evaluation of routine monitoring of the utility systems. Equipment used in support of this system must be maintained in a clean and orderly manner, and located so as to facilitate proper cleaning and maintenance. The audit of this system should include review of procedures and records of calibration and maintenance, verification that the firm is following procedures and that the procedures conform to the manufacturer's recommendations and/or user manuals, and determination of any new equipment added, or if any modifications to existing equipment were made since the last inspection.

C. INSPECTION COVERAGE

For each of the six systems defined above, the inspection must include, coverage of the following three critical elements: **(1) procedures, (2) training/personnel,** and **(3) records**. Actual observations of the processes applicable to each system should be performed whenever possible. Because most products covered by this program are aseptically processed, inspectional guidance for coverage of facilities, equipment calibration, and equipment maintenance has been incorporated into the systems, as appropriate.

1. Standard Operating Procedures (SOPs)

For each of the six-systems the firm should have approved written procedures and associated records, e.g., testing, maintenance, cleaning, etc., that document adherence to the procedures. Investigators should verify through actual observation, whenever possible, whether or not the firm adheres to the approved written procedures.

- Determine if the SOPs include all steps to be followed in the processing, testing, labeling, and distribution of biological drug products.
- Verify the most current version of approved SOPs is readily available for use by key personnel in the areas where the procedures are performed.

2. Training/Personnel

The organization and personnel, including appropriate qualifications and training employed in any given system, should be evaluated as part of that system's operation.

- Determine if the firm has an adequate number of trained personnel, including supervisory, for all assigned functions and operations, for each of the six systems.
- Verify that all personnel responsible for supervising, processing, testing, packing, and distribution of biological drug products have the appropriate educational background, training and experience, including professional training as necessary, or any combination thereof, to perform their assigned functions. Training should also include CGMP regulations, as necessary; to ensure the final product has the safety, purity, potency, identity and effectiveness it purports or is represented to posses.
- If review of the facility's discrepancy reports reveals recurring problems associated with one or more particular employees, review the relevant training records.

3. Records

Records must be maintained concurrently with the performance of each significant step in the processing, testing, and distribution of biological drug products so all steps can be clearly traced

and documented. If any records, which are required by regulation, are maintained in an electronic format in place of paper format, the record keeping system should comply with 21 CFR Part 11 (see Guidance for Industry, Part 11, Electronic Records; Electronic Signatures – Scope and Application, August 2003).

- All records must be legible and indelible, and must identify the person performing the work, including dates of the various entries; show test results as well as the interpretation of results; show the expiration date assigned to specific products; and be as detailed as necessary to provide a complete history of the work performed.
- Review a sampling of records for operations performed in each system, verify that records are complete and maintained as required, and are related to the history and disposition of all products produced and distributed. Verify that the firm routinely reviews records pertinent to the manufacture of lots or units prior to their release or distribution.
- Review records related to product recall, product deviations, complaints, out of specification results, rejects, and failure investigations.

D. INSPECTION APPROACHES

This compliance program provides two surveillance inspection options, Level I, and Level II; both the Level I and Level II option satisfy the biennial inspection requirement.

Level I Inspection Option

The Level I option is a surveillance or compliance inspection that is meant to provide a comprehensive evaluation of the establishment's overall compliance with applicable CGMP requirements.

Level I inspections apply to one or more of the following conditions:

- Initial inspection of a firm
- Firms that have a history of fluctuating compliance problems
- Compliance follow-up inspections
- Firms under a Consent Decree of Permanent Injunction
- Firms under Notice of Intent to Revoke and/or other administrative actions
- A firm that has implemented any significant changes since the prior inspection
- After conducting two previous inspections under a Level II option

The Level I option includes an in-depth audit of the three critical elements in each of the six systems.

If investigators observe serious deficiencies in one or more systems during the course of the inspection (such as those listed in Part V), they should consult with an ORA/OE Compliance Officer, as appropriate, to determine the scope and depth of the inspection, and the necessary documentation to support a possible enforcement action.

Level II Inspection Option

The Level II option is a focused surveillance CGMP inspection that covers **three** of the six key systems, and provides verification of an establishment's continued compliance with CGMP.

This option also includes inspectional coverage of any significant changes to the facilities, manufacturing process, equipment, or license supplements since the preceding inspection.

The Level II option includes an in-depth audit of the three critical elements of the following **two mandatory** systems: (1) **Quality System,** and (2) **Production System; one additional** system must be selected for coverage during the inspection, which will be determined during work planning. Coverage of additional systems should be rotated in successive Level II inspections, unless otherwise indicated *by issues identified during the current or previous inspection*. In addition, during the course of a Level II inspection, verification of QA activities may require limited coverage of other systems.

Select a Level II Option for any one of the following situations:

- The establishment has a satisfactory history of compliance, e.g., at least two successive NAI or VAI inspections
- One of the two previous biennial inspections was a Level I inspection. Note: A comprehensive inspection performed under the previous, non-systems based inspection programs can be considered a Level 1 inspection.
- The inspection preparation procedures revealed no specific trends that may have a significant impact on product safety or quality identified during inspection preparation (review of BPDs, product recalls, etc.).

Note: Significant objectionable conditions identified while conducting a Level II inspection, may prompt coverage of additional systems or change to a Level I inspection, as appropriate. Consult with the ORA/OE Compliance Officer, as appropriate, for guidance in determining the scope and depth of the inspection, and the necessary documentation to support a possible enforcement action.

E. INSPECTIONAL GUIDANCE

1. Cooperative Manufacturing Arrangements:

For further guidance, see: http://www.fda.gov/CBER/Gdlns/coopmfr.htm.

SHARED MANUFACTURING

In a shared manufacturing arrangement, each manufacturer is licensed to perform part of the manufacturing of a product, but no one manufacturer is licensed for the entire process. Each manufacturer in a shared arrangement submits a separate license application, and the approval of the product is based on information from each application.

The manufacturer who prepares the product in its final form will be held responsible for any post-approval obligations, such as reporting biological product deviations and adverse events, unless the manufacturers agree and the approved application says otherwise. Investigators should determine if the agreements in the applications are being met, particularly as they pertain to the integrity of the product.

DIVIDED MANUFACTURING

In a divided manufacturing arrangement, each manufacturer is licensed to manufacture a product in its entirety, but each performs only part of the process. This arrangement is described in

supplements submitted to each manufacturer's license. The record requirements for divided manufacturing arrangements are described in 21 CFR 600.12(e). Each manufacturer must have documentation of its responsibility for manufacturing the product.

The manufacturer who makes the product in final form must retain a complete set of manufacturing records for all operations relating to the product, including those operations performed at another facility. Investigators should thoroughly review the divided manufacturing arrangement and determine if the process; as described in the application supplements, is being followed. Particular attention should be paid to the conditions under which intermediate product is shipped between the facilities, to ensure the integrity of the product.

CONTRACT MANUFACTURING

A license holder is responsible for compliance with product and establishment standards, but may contract out part or all of the manufacturing to another facility. Establishments may hire contractors to perform many manufacturing operations, e.g., testing samples, filling and storing products. Both the manufacturer and contractor share responsibility for product quality; however, the manufacturer remains ultimately responsible. The contractor is responsible for complying with CGMPs, as applicable.

During the inspection, review a copy of the current contract and determine: (1) extent of services provided; (2) each party's responsibility for the product or operations performed; (3) who prepared the SOPs used by the contractor, and (4) who performed product quality control tests. If inspecting a contract manufacturer, verify that the license holder is notified of any manufacturing deviations and any manufacturing changes for its licensed product(s). If inspecting the license holder, who is responsible for final lot release, verify that all records associated with lot release of any given batch are available and have been approved.

2. Change Reporting

For further guidance see: http://www.FDA.gov/CBER/gdlns/chbiol.htm; http://www.FDA.gov/CBER/gdlns/chbiosyn.htm

Requirements that manufacturers notify FDA about all changes in the product, production process, quality controls, equipment, facilities, responsible personnel or labeling, from that in their approved license application are described in 21 CFR 601.12. Determine if process changes made since the approval of the application have been properly reported.

If products are reprocessed or reworked, they must be reported in a supplement to CBER prior to distribution, unless the reprocessing or reworking was done according to a procedure previously approved by CBER. The type of notification is based on the potential risk of the change having an adverse effect on the identity, strength, quality, purity, or potency of the product as it may relate to the safety or effectiveness of the product.

Changes that have a minimal effect on the safety or effectiveness of a product may be implemented before being reported to CBER; however, manufacturers are required to include such changes in their annual reports to the agency.

Data relevant to changes reported in annual reports (e.g., validation data) must be made available during FDA inspections. When a change has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as it may relate to the safety or

effectiveness of a product, a manufacturer must submit a license supplement describing the change. If FDA does not advise the manufacturer within 30 days of submission of the supplement that the change requires approval prior to distribution of the product (i.e., a Prior Approval Supplement), the manufacturer may distribute product manufactured using the change pending approval of the supplement. These supplements are referred to as CBE-30, or changes being effected in 30 days.

When a change has a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the product as it may relate to the safety or effectiveness of the product being manufactured, which uses that change, cannot be distributed until FDA approves a prior approval supplement (PAS) describing the change.

If the firm has an FDA-approved comparability protocol in place for a particular change or set of changes, the firm may be able to report the change in a lower reporting category that would be set forth in the approved comparability protocol supplement, if it follows the protocol when implementing the change.

For example, if a change would normally be reported as a prior approval supplement, the firm could report it in a CBE-30 supplement, if they have an approved comparability protocol for that change that sets forth a reduced reporting category, and the protocol was followed when making and evaluating the change.

When evaluating changes to an approved application:

- Request a complete list of changes or modifications made to products, processes, quality control, equipment, facilities, systems, and/or responsible personnel that have not been submitted to CBER as either a supplement or in an annual report since the last inspection; include it as an exhibit in the report.
- Review any changes for which the manufacturer determined a supplement is not required, and that have not been included in an annual report to CBER.
- Determine if changes have been validated, when appropriate. If there is any question as to whether or not a change should have been reported or whether a change should have been submitted in a supplement instead of an annual report, contact OCBQ/DIS, or the appropriate product office.

Note: Manufacturer's annual reports are submitted based on the specific product approval date, indicated in 21 CFR 601.12(d). Therefore, the annual reporting time varies for any given product or company.

3. Components

Manufacturers who purchase components from outside sources are required to establish adequate specifications for such components. The licensed manufacturer is ultimately responsible for ensuring that components it uses conform to specifications and are acceptable for use. This may be done through inspections, sampling and testing, and/or through certificates of analysis from the supplier. The manufacturer should establish the validity of the certificates through experience, historical data, testing, and/or audits of the supplier.

For components received from outside sources, either purchased or otherwise received, verify that: (1) the firm has written, approved specifications for the component(s); (2) the firm

evaluates and selects suppliers based on their ability to meet specified requirements, and (3) the type and extent of control needed over the component and suppliers has been defined and is based on the manufacturer's evaluation of the supplier.

Animal source material must meet the applicable requirements of 21 CFR 600.11. Investigators should determine if tests and specifications for materials of animal source that may potentially be contaminated with adventitious agents (e.g., mycoplasma, Bovine Spongiform Encephalopathy for bovine-derived products, and others) are performed as described in the license application.

Acceptance activities must be documented. Verify that the manufacturer has defined methods, e.g., inspections, tests, and other verification tools (certificates of analysis and/or supplier audits), to ensure that components conform to all specifications prior to release for use in manufacturing and that acceptance activities are documented in the batch record. Review the manufacturing SOPs and batch records for a representative number of lots to ensure that acceptance criteria are met for all components.

Media/Buffers

The firm should have well-established acceptance criteria for all materials. If buffers or media are prepared prior to use, determine if the firm has established and validated holding times and conditions, and has records to show the conditions are met.

Containers/Closures

Determine if the firm has adequate written specifications and procedures describing the receipt, handling, sampling, and storage of containers and closures, especially those that need to be sterile and/or pyrogen-free.

4. Validation:

Process

Validation data for the manufacturing process are generally reviewed during application review, as are the validation data to support changes that are reported in prior approval supplements. Determine if any changes in the process made since the approval of the application, for which a supplement is not required, have been validated in accordance with a protocol, and that the validation process is adequately documented.

Computer

If the firm uses computer systems to control any part of the process, determine if the software for computers and automated data processing systems are validated. If the firm is using a computerized record-keeping system, ensure the integrity of records is maintained. The systems should be such that records cannot be overwritten to disguise failing results. Document any computer systems the firm uses for control of the manufacturing process.

Shipping

Determine if shipping conditions have been validated, including containers and methods. If the firm has contract manufacturers that perform some or all of the manufacturing steps, verify that

shipping conditions for the partially processed materials have been validated, and the validated processes are followed and documented. The shipper must verify the product is maintained at the proper temperature during shipment, and must have records to demonstrate this.

5. Lot Release

Per 21 CFR 610.2(a), a manufacturer may be required to send samples of any lot of any licensed biological product, together with protocols showing results of applicable tests to CBER. It further states that upon notification by the Director, CBER, a manufacturer shall not distribute a lot of a product until the Director releases it.

Some manufacturers of well-established biological drug products have, through approved license supplements; *been granted the alternative to* lot release and are on a "Surveillance" program. Manufacturers on surveillance are still required to submit samples and/or protocols to CBER at specified intervals, but they may distribute the applicable products without receiving prior CBER lot release. Such manufacturers must still complete their own internal lot release process whether on CBER lot release or on a surveillance program.

The Director, CBER, at any time, including as a result of compliance history or regulatory actions, may remove a product from surveillance and return it to CBER lot release.

Review representative lot release test records to verify all specifications have been met. Compare raw test data against test results provided in protocols submitted to CBER to determine if they correlate. Check whether any lot has failed to be released, and if so, the reason for the failure and the disposition of all failed lots.

6. Biologic Product Deviations (BPDs)
For further guidance see: http://www.fda.gov/cber/biodev/biodev.htm

Under 21 CFR 600.14, a manufacturer must report any event associated with the manufacturing, including testing, processing, packing, labeling, or storage, or with the holding or distribution of a licensed biological product, which may affect the safety, purity, or potency of a **distributed** licensed product.

BPDs are required to be reported to the CBER/OCBQ/DIS as soon as possible, but no later than 45 calendar days from the date of discovery of information reasonably suggesting a reportable event has occurred. Under 21 CFR 600.14, the manufacturer who holds the biologics license and who had **control** over the product when the deviation or unexpected event occurred must report a BPD.

If a manufacturer contracts out any manufacturing step, that manufacturing step is performed under the manufacturer's control under the regulation. Thus, under 21 CFR 600.14(a), the manufacturer must establish a procedure for receiving information from that contract manufacturing facility on all deviations, complaints, and adverse events that may affect the product.

A *contract manufacturer* (i.e., performs, under contract, a step in manufacturing for another facility) must conduct manufacturing in accordance with all applicable regulations.

*CBER provides ORA with direct access to BPD information through CEARS (CBER Error and Accident Reporting System). CEARS only captures the reportable events. Instructions for accessing the system are found on the CEARS intranet web page.

*To facilitate industry reporting of BPD, CBER developed a standardized reporting format (FDA Form 3486) with both hard copy and electronic reporting. CBER encourages electronic reporting.

*Prior to conducting an inspection, investigators should review the manufacturer's BPD submissions in CEARS. An assessment of the deviation codes may assist you in determining the optional system to inspect. Otherwise, select a representative sample of reports to verify the adequacy of the firm's corrective action.

- *Evaluate both reportable deviations and non-reportable incidents or problem reports and verify the adequacy of any corrective action implemented by the manufacturer.
- *Determine if the manufacturer filed all reportable biological product deviations.

It is FDA policy to only cite on a Form FDA-483 a deficiency associated with a previously-reported BPD if the establishment's investigation or corrective action was inadequate.
**

7. Reporting of Adverse Experiences

Under 21 CFR 600.80, any life-threatening adverse experience, serious adverse experience, and unexpected adverse experience associated with the use of a biological product in humans, whether or not considered product related, must be reported by the manufacturer to CBER as soon as possible and no later than 15 days of initial receipt of information, and periodically, depending on the seriousness of the adverse reaction. Manufacturers of blood products, including plasma derivatives, are required to submit monthly reports for adverse experiences involving transmission of infectious diseases. Review records of adverse events received by the manufacturer, and determine if reports have been submitted to CBER as required. Contact OCBQ/DIS if there are questions or concerns regarding the reportability of an adverse experience.

F. REPORTING

Note: If, at any time during the inspection, it is determined that a potentially serious health hazard exists, investigators and compliance officers should contact CBER's OCBQ/DCM immediately.

Form FDA 483

Record any deviation from 21 CFR Parts 210-211 or Parts 600-680, including failure to adhere to license and supplement requirements, on the FDA 483. Per the IOM, conditions listed on the FDA 483 should be **significant,** and should **relate** to an observed or potential problem with the facility, equipment, processes, controls, products, employee practices or records.

"Potential problems" should have a reasonable likelihood of occurring based upon observed conditions, records or events. Do not cite on the FDA 483 deviations from draft or proposed regulations or from guidance documents Present verifiable evidence for conclusions of observed

non-compliance with CGMPs. Investigators should not use the term "inadequate" without explaining why or how it is inadequate. Refer to policy in the IOM, Chapter 5, Section 512 and Field Management Directive 120 for further guidance on the content of Inspectional Observations.

Organize inspectional observations under separate '**system**' captions as defined in this program. List observations in order of importance within each system. Similar or repeated observations should be consolidated under a unified observation. Deficiencies that were noted during a previous inspection and remain uncorrected should be included on the FDA 483 as repeat deficiencies. Discuss with manufacturer prior observed deficiencies that have gone uncorrected.

If necessary, contact the ORA/OE CO to discuss and resolve questions relating to the possible inclusion of observations on the FDA 483. Good judgment is necessary when deciding whether conditions are objectionable in view of their relation to other conditions or controls at the given time and place. When there is continued uncertainty about the significance of one or more observations, they should not be listed on the FDA 483. They should, however, be discussed with the firm's management, and reported in the EIR.

Systems

Report briefly on all systems covered as outlined in PART III, INSPECTIONS, of this program, regardless of findings. If the inspection is a follow-up to a violative inspection, report on the implementation of the firm's promised corrective actions.

Imported Products
Examine, report, and track counterfeit imported products, returned and rejected imported products, and complaint files concerning imported products.

Report Preparation and Classification

The Team Biologics **lead investigator will coordinate the preparation of the report. The report will be endorsed and classified by the investigator.

The ORA/OE CO will have the initial responsibility to review *domestic* OAI reports, and will decide which reports should be presented to CBER/OCBQ for regulatory action consideration. The ORA/OE CO has the authority to independently re-classify an inspection conclusion from OAI to VAI or NAI.

For those reports sent to CBER/OCBQ for regulatory action consideration, CBER/OCBQ's Division of Case Management (DCM) will make the final classification determination.

Reports should be submitted within established agency time frames.

Part IV – ANALYTICAL

NO FIELD ANALYSES ARE PLANNED UNDER THIS PROGRAM.

The routine collection and analysis of physical samples is not envisioned under this program. If CBER requests sample collection, specific instructions will be provided. Consult with CBER program contacts identified in Part VI, **before** collecting samples for agency analysis, except for documentary samples for interstate commerce (collect a documentary sample in accordance with IOM 405.02 to support regulatory/administrative action).

Contact the CBER Sample Custodian **(301-594-6517)** before shipping any samples to CBER. No one is available to receive samples over the weekend. All samples collected under this program will be shipped to:

Center for Biologics Evaluation and Research
Attention: Sample Custodian, HFM-*672*
5516 Nicholson Lane, Building B, Room 113
Kensington, MD 20895

Collect any samples of a potentially bio-hazardous nature in accordance with IOM 145.

Original results of analyses will be forwarded to the ORA/OE CO, with a copy to the home district of the involved facility. Investigators should *document in FACTS* to whom *CBER should send* the sample results. *If unable to document in FACTS, then use Form FDA 464A, C/R Continuation Sheet.*

Copies of collection reports for physical samples must be submitted to CBER/OCBQ/DCM, HFM-610.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

The evaluation of inspection findings and any resultant recommendation for enforcement action will be conducted in accordance with existing procedures and the RPM. The Team Biologics Core Team will ensure the home district will be advised of inspectional and compliance activities related to facilities located within the district.

The decision on the type of action to recommend should be based on the seriousness of the documented deficiencies, and the most effective way to protect the public health. Because the number of manufacturers of biological drug products (vaccines, allergens, etc.) is often small, medical need and relative availability of the product(s), as well as the potential adverse effect of the CGMP deficiencies on the finished product(s) should be considered when determining the appropriate advisory, administrative or judicial action.

A firm's written corrective action, in response to the FDA 483, **should not** preclude the consideration of an advisory, administrative, or judicial action. If the objectionable observations represent a continuing pattern of non-compliance, a failure to correct significant deficiencies noted during a previous inspection, or the deficiencies pose a serious threat to the public health, and voluntary action is either not appropriate or can not be readily accomplished, the appropriate advisory, administrative, or judicial action should be recommended.

State of Control

A firm is considered to be operating in a **state-of-control** when it employs conditions and practices that ensure compliance with the intent of Section 501(a)(2)(B) of the Act, and the portions of the CGMP regulations that pertain to their systems. A firm in a state of control produces finished biological drug products for which there is an adequate level of assurance of quality, strength, identity, purity, and potency.

Well-documented CGMP deficiencies provide the evidence for concluding that a firm is not operating in a state of control. Evidence of serious deficiencies within a system could constitute overall failure of that system, and the firm to be considered **not** in a **state-of-control**. When the inspectional findings demonstrate that a firm is not operating in a state of control, and/or the establishment's management is either unwilling or unable to implement full corrections in a timely manner, administrative or judicial action should be considered.

Regulatory recommendations should be based on serious deficiencies that are well documented with supporting evidence. The quality of any action begins with the quality of evidence collected at the time of the inspection, to support the observed objectionable conditions. The recognition, collection, and effective presentation of evidence are essential to any successful advisory, administrative, or judicial action. Establish individual responsibility, and identify persons to hold accountable for violations and with whom the agency should communicate to seek lasting corrections, and/or to be the subject of enforcement actions.

Refer to the RPM to determine the appropriate advisory, administrative or judicial action based on the inspectional findings. Early consultation with CBER/OCBQ/DCM is critical when immediate action is indicated, e.g., license suspension, a temporary restraining order (TRO), etc. See RPM Chapter 6 regarding an injunction to protect the public health.

When inspectional findings indicate the potential for fraud, e.g., falsification, counterfeiting, illegal importation, and/or drug diversion, the investigator should notify the Team Biologics Compliance Officer, the Team Biologics Core Team Leader, and OCBQ/DCM (HFM-610), who will alert the appropriate OCI office. The investigator should continue to pursue any public health concerns, in coordination with CBER/OCBQ, concurrently.

An initial decision on the type of action to recommend should be consistent with the RPM and be based on the seriousness and frequency of the deficiencies as well as the firm's overall compliance history. For example, classify an inspection report that documents one or more systems **not** in a **state-of-control** as OAI, and consider recommending a Warning Letter or taking other appropriate action.

For a licensed biologic, the advisory, administrative, and judicial options available are listed in Table 1.

Table 1: Table of Available Advisory, Administrative, and Judicial Options

Action	**Among other things, consider if,**
Warning Letter	Violations of regulatory significance that cause one or more systems to be considered not in a state-of-control.
License Revocation (21 CFR 601.5)	Notice of Intent to Revoke with Opportunity for Correction: Unable to gain access to the manufacturing facility for inspection Licensed products are not safe or effective for their intended use, or are misbranded with respect to any such use. Manufacturer fails to report a change in accordance with 21 CFR 601.12 Manufacturer fails to conform to applicable standards to ensure product safety, potency and purity Licensed products are no longer manufactured Direct Revocation without Opportunity for Correction: Demonstration of willful disregard in addition to above.
License Suspension (21 CFR 601.6)	Reasonable grounds for revocation and a danger to health exist. It provides immediate withdrawal of the authorization to ship a biological product in interstate commerce.
Seizure	Manufacturer is unwilling or unable to retrieve violative products, or products held for sale are unsuitable for safe use. U.S. Marshal takes possession of products through Court Order pursuant to Section 304 of the Federal Food, Drug, and Cosmetic Act.
Injunction	A current health hazard exists, the establishment has a history of uncorrected violations despite previous warnings, suspension of the firm's license would result in an unacceptable shortage of products, and/or to halt intrastate distribution of products manufactured under violative conditions
Prosecution	Fraud, gross, flagrant or intentional violations, health hazards, or serious violations that have not been corrected.

Deficiencies

The investigator should verify through actual observation, whenever possible, whether or not the firm adheres to the applicable regulations and the law. The following, although not all-inclusive, are examples of deficiencies that may be indicative of the firm's **state-of-control**.

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

Examples of deficiencies are arranged by System. Any deficiency listed in one system may be applicable to other systems. For example, deficiencies pertaining to the training and qualification of employees, or deficiencies involving discrepancy and failure investigations, are listed only under the Quality System. However, both deficiencies could be applicable to multiple systems. In addition, while the CGMP regulations apply to the manufacture of biological drug products, the same CGMP principles apply for the manufacture of biological intermediates and drug substances under Section 501(a)(2)(b) of the FD&C Act, and the Biologics regulations under 21 CFR Part 600.

Quality System

Firms must have an effective quality assurance program, and should not rely solely on finished product testing to ensure products meet their specifications. The responsibilities and functions of the quality control unit must be clearly defined. QA is not limited to processing and finished products, but incorporates all the major systems, e.g., components and in-process materials, facilities and equipment, complaint handling, failure investigation, and change control.

- Training/qualification of employees
  - *Employees [are/were] not trained in the particular operation that they performed and/or in CGMPs related to their job functions. 211.25(a)*
  - *Individuals engaged in the manufacture, processing, and packing of products [do/did] not have education, training, and experience, or any combination thereof, to enable them to perform assigned functions. 211.25(b), 600.10(b)*
  - *There [are/were] not an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each product. 211.25(c)*

- Product reviews by the quality control unit, at least annually
  - *The quality control unit [fails(ed)] to review production records to assure that no errors has occurred, or if errors have occurred that they are fully investigated. 211.22(a)*
  - *The quality control unit [fails(ed)] to conduct and/or document an annual review of production records so that data therein can be used for evaluating the quality standards of each product to determine the need for changes in product specifications, manufacturing and/or control procedures. 211.180(e)*
  - *Written procedures for production and process control [are/were] not drafted, reviewed and approved by the appropriate organizational units and/or the quality control unit. 211.100(a)*

- Complaint reviews; documented, evaluated, and investigated including corrective action and follow-up where appropriate
  - *Written procedures [are/were] not established and/or followed for the annual review and evaluation of complaints and investigations. 211.180(e)(2)*
  - *Written procedures [fail(ed)] to include provisions for review by the quality control unit of complaints involving the possible failure of the product to meet any of its specifications and, a determination as to the need for an investigation. 211.198(a)*
  - *The compliant investigation [does/did] not include documentation of the findings and/or follow-up. 211.198(b)(2)*

- Discrepancy and failure investigations related to manufacturing and testing; documented, evaluated, and thoroughly investigated, including corrective actions and follow-up where appropriate
  - *Failure to conduct investigations into unexplained discrepancies or*

- *The failure of a batch or any of its components to meet specifications whether or not the batch was distributed.*
  - *[Are/were] not always documented*
  - *[Do/did] not always include the conclusions and/or follow-up*
  - *[Do/did] not always extend to other batches of the product*
  - *[Do/did] not always extend to other products with the associated discrepancies 211.192*

- Adherence to an adequate Out of Specification (OOS) procedure
  - *Deviations from the written procedures [are/were] not recorded and/or justified. 211.160(a)*
  - *Failure to conduct investigations into unexplained discrepancies or the failure of a batch or any of its components to meet specifications: 211.192*

- Change control procedures; documented, evaluated, approved, and the need for revalidation assessed by the quality control unit.
  - *The quality control unit [fails(ed)] to:*
    - *Approve or reject all procedures and/or specifications impacting on the identity, strength, quality, and purity of the products. 211.22(c)*
    - *Draft, review, and/or approve written procedures, including any changes. 211.100(a)*
    - *Conduct and/or document an annual review of production records. 211.180(e)*

- Reprocessing and/or reworking procedures; evaluated, reviewed and approved by the quality control unit, and the impact on validation and stability evaluated
  - *Written procedures [are/were] not established and/or followed for reprocessing batches of products, and [do/did] not include the steps to be taken to assure that the reprocessed batches conform to all established standards, specifications, and characteristics. 211.115(a)*
  - *Reprocessing procedures [are/were] not performed with the review and approval of the quality control unit. 211.115(b), 601.12*

- Returned and salvaged product; assessment and investigation conducted and expanded where warranted, including disposition
  - *Written procedures [are/were] not established to assure that the responsible officials of the firm are made aware of returned and/or salvaged product, and are notified in writing of any investigations conducted. 211.180(f)*

- Product rejects investigated with corrective action where appropriate
  - *Failure to establish and/or follow written procedures for the receipt, identification, storage, handling, sampling, testing; and approval or rejection of components and product containers and closures. 211.80(a)*
  - *Products that [fail(ed)] to meet established standards or specifications and any other relevant quality control criteria [are/were] not rejected. 211.165(f)*
  - *Failure to conduct investigations into unexplained discrepancies or the failure of a batch or any of its components to meet specifications. 211.192*

- Stability failures; investigation
  - *Failure to conduct investigations into unexplained discrepancies and/or the failure of a batch or any of its components to meet specifications. 211.192*
  - *The quality control unit [fails(ed)] to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. 211.22(a)*

- Quarantine products
  - *Failure to:*
    - *Ensure that rejected components, product containers, and closures [are/were] identified and controlled under a quarantine system to prevent their use in manufacturing or processing operations for which they are unsuitable. 211.89*

- *Establish and/or follow written procedures that describe the warehousing of products, including quarantine before release. 211.42(a)*

- Finished product distribution records by lot
  - *Failure to establish and/or implement a system by which the distribution of each lot of product could be readily determined to facilitate its recall if necessary. 211.150(b)*
  - *Distribution records [do/did] not contain the name and strength of the product and description of the dosage form. 211.196*

- Adverse Experience Reporting (AER)
  - *AERs [are/were] not submitted to CBER, and/or reviewed as required. 21 CFR 600.80*

- Licensing
  - *Significant manufacturing changes [are/were] not reported and [are/were] implemented, and product [is/was] distributed prior to obtaining the required CBER approval. 601.12(b)*
  - *Product [is/was] not manufactured as described in the approved license application. 601.2(d)*

NOTE: Consult with CBER/DIS before including observations on the Form FDA 483, or in an enforcement action recommendation, that are related to non-conformity with commitments made in the Biologics License Application.

- Reporting of Biological Product Deviations (BPDs)
  - *Reportable BPDs [are/were] not submitted to CBER, or [are/were] not submitted within the required timeframe. 600.14*

Facilities and Equipment System

Deficiencies in this system may include violative conditions relating to the design, maintenance and cleaning of the facility and equipment, including but not limited to air handling and water systems, lighting, and sanitation.

FACILITIES:

- Maintenance
  - *Buildings used in the manufacture, processing, packing, or holding of products [are/were] not maintained in a state of good repair. 211.58*

- Facility design and air handling systems for prevention of cross-contamination (e.g., cytotoxics, live virus, spore forming organisms)
  - *Building(s) used in the manufacture, processing, packing, or holding of a product [are/were] not of suitable size, construction and/or location to facilitate cleaning, maintenance, and proper operations. 211.42(a)*
  - *Operations [are/were] not performed within specifically defined areas of adequate size. 211.42(c)*
  - *Floors, walls, and ceilings of aseptic processing areas are not smooth, hard surfaces that are easily cleanable. 211.42(c)(10)*

- General air handling systems
  - *Adequate ventilation [is/was] not provided. 211.46(a)*
  - *Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature [are/were] not provided. 211.46(b), 600.11(a)*
  - *Air filtration systems, [are/were] not used, when appropriate, on air supplies to production areas. 211.46(c)*

- Specifically designed area for the manufacturing operations performed by the firm to prevent contamination or mix-ups
  - *Buildings [do/did] not have adequate space for the orderly placement of equipment and materials to prevent mix-ups and/or contamination between different components, product containers, closures, labeling, in-process materials, and/or products. 211.42(b)*
  - *There [are/were] not separate or defined areas or other control systems for the firm's operations as necessary to prevent contamination or mix-ups, including:*
    - *Receipt, identification, storage, and withholding from use of components, product containers, closures, and labeling pending sampling, testing, or examination by the quality control unit before release for manufacturing or packaging*
    - *Holding of rejected, and storage of released components, product containers, closures, and labeling before disposition*
    - *Storage of in-process materials*
    - *Manufacturing and processing operations*
    - *Quarantine storage before release of products*
    - *Control and laboratory operations*
    - *Aseptic processing, including:*
      - *An environmental monitoring system*
      - *A room and equipment cleaning/disinfecting system*
      - *A maintenance system for equipment used to maintain aseptic conditions. 211.42(c)*
      - *Laboratory and bleeding rooms used for the processing of products [are/were] not effectively fly-proofed and kept free of flies and vermin. Rooms [are/were] not constructed as to assure the freedom from dust, smoke, and other deleterious substances and to permit thorough cleaning and disinfection. 600.11(c)*

- Sanitation of the building, use of rodenticides, fungicides, insecticides, cleaning and sanitizing agents
  - Buildings used in the manufacture of products [are/were] not:
    - *Maintained in a clean and sanitary condition. 211.56(a)*
    - *Free of infestation by rodents, birds, insects, and other vermin. 211.56(a)*
  - *Written sanitation procedures:*
    - *[Are/were] not established for the use of suitable rodenticides, insecticides, fungicides, and fumigating agents. 211.56(c)*
    - *[Are/were] not designed to prevent the contamination of equipment, components, product containers, closures, packaging, labeling materials, or products. 211.56(c)*

<u>EQUIPMENT:</u>

- Adequacy of equipment design, size, and location
  - *Equipment used in the manufacture of the product [is/was] not of appropriate design, adequate size, and/or suitably located for its intended use and/or for its cleaning and maintenance. 211.63*

- Equipment surfaces should not be reactive, additive, or absorptive
  - *Equipment is constructed so that surfaces that contact components, in-process materials, or products are reactive, additive, and/or absorptive and may alter the safety, identity, strength, quality, or purity of the product. 211.65(a)*

- Appropriate use of substances required for equipment operations (lubricants, coolants, refrigerants, etc.) contacting products/containers/etc.
  - *Equipment is constructed so that substances required for operation, such as lubricants or coolants, come into contact with components, product containers, closures, in-process materials, or products and may alter the safety, identity, strength, quality, or purity of the product. 211.65(b)*

- Equipment cleaning and use logs

- *A written record of major equipment cleaning, maintenance, and use [is/was] not included in individual equipment logs that show the date, time, product, and/or lot number of each batch processed. 211.182*

- Cleaning procedures and cleaning validation
  - *Written procedures for cleaning and maintenance of equipment, including utensils, used in the manufacture of the product [are/were] not established and/or followed. 211.67(b)*
  - *Equipment and/or utensils [are/were] not cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the product. 211.67(a)*
  - *Records of equipment maintenance, cleaning, sanitizing, and inspection [are/were] not kept. 211.67(c)*

- Equipment qualification, calibration and maintenance, including computer qualification/validation and security
  - *Equipment [is/was] not routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of calibration checks and inspections [are/were] not maintained. 211.68(a)*
  - *Appropriate controls [are/were] not exercised over computer or related systems to assure that only authorized personnel institute changes in master production and control records or other records. 211.68(b)*
  - *Input to and output from the computer or related system of formulas or other records or data [are/were] not checked for accuracy. 211.68(b)*
  - *Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss are not maintained. 211.68(b)*

- Equipment identification practices (where appropriate)
  - *Major equipment used during the production [is/was] not properly identified. 211.105(a)*

Materials System

Deficiencies in this system may include violative conditions relating to material handling, including, but not limited to, in-process materials and finished product examination, sampling, testing, quarantine, storage, issuance of materials, including containers and closures, and discrepancy investigation and appropriate follow-up.

- Identification, Inventory and Storage of components, containers, closures
  - *Written procedures [are/were] not established, and/or followed for the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and product containers and closures. 211.80(a)*
  - *Each lot of product containers [is/was] not identified with a distinctive code or status (e.g., quarantined, approved, or rejected*). *211.80(d)*
  - *The components, product containers and/or closures [are/were] not handled and/or stored in a manner to prevent contamination. 211.80(b)*

- Storage under quarantine until tested or examined, and released
  - *The components, product containers, and/or closures [are/were] not stored under quarantine until they were released. 211.82(b)*
  - *The product containers and/or closures [are/were] not withheld from use, and/or were released for use by the quality control unit before the lots had been sampled and tested by the quality control unit. 211.84(a)*

- Representative samples collected, tested or examined using appropriate means
  - *A representative sample of each shipment of each lot of components [is/was] not collected for testing or examination. 211.84(b)*

- At least one specific identity test is conducted on each lot of each component
  - *Tests [are/were] not conducted to verify the identity of each component of a product. 211.84(d)(1)*

- A visual identification is conducted on each lot of containers and closures
  - *The product containers and/or closures [are/were] not examined visually for container damage or broken seals upon receipt or before acceptance. 211.82(a)*

- Testing or validation of supplier's test results for components, containers and closures
  - *Written specifications for each component [does/did] not include:*
    - *Testing for conformity with all appropriate written specifications*
    - *In lieu of such testing, a report of analysis from the supplier of the component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. 211.84(d)(2)*
  - *Written specifications for each container and closure [does/did] not include:*
    - *Testing for conformity with all appropriate written procedures*
    - *In lieu of such testing, a certificate of testing from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals. 211.84(d)(3)*
    - *The written procedures for examination and testing components [does/did] not include established specifications for contamination. 211.84(d)(5)*

- Rejection of any component, container, closure not meeting acceptance requirements
  - *Failure to reject lots of material that did not meet specifications. 211.84(e)*

- Appropriate retesting/reexamination of components, containers, closures
  - *After prolonged storage in an uncontrolled area, the product containers and/or closures were not retested or reexamined and approved by the quality control unit. 211.87*

- Quarantine of rejected materials
  - *Failure to assure that rejected components, product containers, and/or closures [are/were] identified and controlled under a quarantine system designed to prevent their use in operations for which they are unsuitable. (211.89)*

- Water and process gas supply, design, maintenance, validation and operation.
  - *The written specifications for each component [does/did] not include:*
    - *Testing for conformity with all appropriate written specifications*
    - *In lieu of such testing, a report of analysis from the supplier of the component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. 211.84(d)(2)*

- Containers and closures:
  - *The product containers and/or closures could not be shown to be non reactive, additive, or absorptive. 211.94(a)*
  - *Standards or specifications, methods of testing, and methods of cleaning, sterilizing, and processing to remove pyrogenic properties [are/were] not written and/or followed for product containers and closures. 211.94(d)*

Production System

Deficiencies in this system may include violative conditions relating to production activities including, but not limited to, batch processing and control records, reprocessing, in process controls, tests and examinations, equipment cleaning and use logs.

- Written procedures; deficiencies
  - *Written procedures for production and process controls [does/did] not assure that products have the identity, strength, quality, and purity they purport or are represented to possess. 211.100(a)*
  - *Deviations from the written procedures [are/were] not recorded and justified. 211.100(b)*

- Adequate procedure for charge-in of components
  - *Procedures for charge-in of components [do/did] not include:*
    - *Written production and control procedures designed to assure that the products produced, have the identity, strength, quality, and purity they purport or are represented to possess. 211.101*
    - *Formulation of the batch to provide not less than 100 percent of the labeled or established amount of active ingredient. 211.101(a)*
    - *Adequate supervision of component weighing and measuring operations. 211.101(c)*

- Identification of equipment with contents, and where appropriate phase of manufacturing and/or status
  - *All compounding and storage containers, processing lines, and major equipment used during the production of a batch of product [are/were] not properly identified at all times to indicate their contents or, when necessary, their phase of processing of the batch. 211.105(a)*

- Calculation and documentation of actual yields and percentage of theoretical yields
  - *Actual yields and percentages of theoretical yield [are/were] not determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the product. 211.103*

- Batch production and control records
  - *Batch production and control records are/were not prepared for each batch of product and/or [do/did] not include complete information relating to the production and control of each batch. 211.188, 600.12(a)*

- Established time limits for completion of phases of production
  - *Time limits for the completion of each phase of production, to assure the quality of the product, [has/have] not been established. 211.111*

- Implementation and documentation of in-process controls, tests, and examinations
  - *Written procedures that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch [are/were] not established and/or followed. 211.110(a)*

- Justification and consistency of in-process specifications and product final specifications
  - *In-process specifications [are/were] not consistent with product final specifications. 211.110(b)*

- Prevention of objectionable microorganisms in sterile products
  - *Appropriate written procedures, including validation of any sterilization process, designed to prevent microbiological contamination of products purporting to be sterile, [are/were] not established and/or followed. 211.113(b), 600.11(b)*

- Adherence to preprocessing procedures (e.g., set-up, line clearance, etc.)
  - *Production and process control procedures [are/were] not: 211.100(b)*
    - *Written and/or followed for various production and process control functions*
    - *Documented at the time of performance*

- *Deviations from the written procedures [are/were] not recorded and justified.*

- Master production and control records
  - *Master production and control records [do/did] not include: 211.186*
    - *Complete manufacturing and control instructions*
    - *Sampling and testing procedures*
    - *Specifications*
    - *Special notations and/or precautions to be followed*
    - *Written procedures for preparing the master production and control records*

Packaging and Labeling System

Deficiencies in this system may include violative conditions relating to packaging operations, and the handling of labels and labeling including, but not limited to, the receipt, inspection, issuance, and reconciliation of labels, and discrepancy investigation and follow-up

- Acceptance operations for packaging and labeling materials; examination, storage and usage
  - *The procedures describing the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials [are/were] not written and/or followed. 211.122(a)*
  - *Labeling and packaging materials [are/were] not representatively sampled, examined and/or tested upon receipt and before use in packaging or labeling of product. 211.122(a)*
  - *Labeling and/or packaging materials not meeting appropriate written specifications [are/were] approved and released for use. 211.122(b)*
  - *Labels and other labeling materials for each different product, strength, dosage form, or quantity of contents [are/were] not stored separately and/or suitably identified. 211.122(d)*
  - *Printing devices on/or associated with, manufacturing lines used to imprint labeling upon the product unit label or case are/were not monitored to assure that all imprinting conforms to the print specified in the batch production record. 211.122(h)*

- Control of issuance of labeling, examination of issued labels and reconciliation of used labels
  - *Labeling issued for use in product labeling operations:*
    - *[Are/were] not strictly controlled 211.125(a)*
    - *[Are/were] not carefully examined for identity and conformity to the labeling specified in the master or batch production records. 211.125(b)*
    - *The quantities of labeling issued, used, and returned are not reconciled, and/or discrepancies between the quantity of finished product and the quantity of labeling issued [are/were] not evaluated. 211.125(c)*
    - *There is no assurance that all excess labeling bearing lot or control numbers [is/was] destroyed. 211.125(d)*

- Packaging and labeling operations, line clearance, inspection and documentation including validation and security of computerized processes
  - *Written procedures [are/were] not established, and/or not followed, and/or procedures do not assure that correct labels, labeling, and packaging materials are used. 211.130*
  - *Physical or spatial separation [is/was] not adequate to prevent mix-ups and/or cross-contamination from operations on other products. 211.130(a)*
  - *Filled unlabeled product containers that are set aside and held for future labeling operations [are/were] not identified and/or handled to preclude mislabeling of individual containers, lots, or portions of lots. 211.130(b)*
  - *Products [are/were] not identified with a lot or control number that permits determination of the history of the manufacture and control of the batch. 211.130(c)*
  - *Packaging and labeling facilities [are/were] not inspected immediately before use to assure that all products and packaging and labeling materials not suitable for subsequent operations [are/were] removed. 211.130(e)*

- *Equipment used in computerized packaging and/or labeling processes [are/were] not routinely calibrated, inspected or checked according to a written program designed to assure proper performance. 211.68(a)*
- *Changes in the computers and related systems [are/were] not appropriately controlled to assure only authorized personnel performed them. 211.68(b)*

- Control of filled unlabeled containers, later labeled under multiple private labels
  - *There [are/were] no written procedures for the identification and handling of filled product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. .211.130(b)*

- Expiration dating
  - *The product labels: [211.137(a), (d)]*
    - *[Do/did] not bear an expiration date determined by appropriate stability testing*
    - *Have expiration dates that [are/were] not related to storage conditions on the label*
    - *[Do/did] not bear expiration dates for both the reconstituted and lyophilized product*

- Examination of the labeled finished product [211.134(a), (b)]
  - *Labeled finished products,*
    - *[Are/were] not examined during the finishing operations to provide assurance those containers and packages in the lot have the correct label*
    - *[Are/were] not sampled with a representative number of units for visual examination for correct labeling at the completion of finishing operations*
    - *[Do/did] not include documentation of examination operations*

- Complete labeling control records, including specimens or copies of all labeling used
  - *Records [are/were] not maintained for each shipment of each different labeling and packaging material indicating receipt, examination or testing. 211.122(c)*
  - *Records documenting the examination and review of labels and labeling for conformity with established specifications [are/were] not maintained. 211.184(d)*
  - *Batch production and control records [do/did] not include complete labeling control records including specimens or copies of all labeling used. 211.188(b)(8)*

Laboratory Control System

Deficiencies in this system may include violative conditions relating to laboratory functions including, but not limited to, staffing, facilities, calibration and maintenance of equipment, specifications and standards, sampling plans and testing methodology.

- Written procedures and control system for laboratory operations
  - *Specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, including any changes, [are/were] not drafted by the appropriate organizational unit and/or reviewed and approved by the quality control unit. 211.160(a)*

- Calibration and maintenance programs for analytical instruments and equipment
  - *There [are/were] no written procedures, or procedures are not followed for the calibration of instruments, apparatus, gauges, and recording devices at suitable intervals containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. 211.160(b)(4)*

- Adherence, validation/verification to the written methods of analysis
  - *There [are/were] no written procedures describing method of sampling and the number of units per batch to be tested. 211.165(c)*

- *The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm [are/were] not established and/or documented. 211.165(e)*

- Testing and release for distribution
  - *Laboratory testing [does/did] not determine conformance to final specifications, including identity and strength of each active ingredient, prior to release of each batch of product 211.165(a)*
  - *Appropriate laboratory testing [is/was] not performed for each batch of product required to be free of objectionable microorganisms. 211.165(b)*

- Specifications, standards, and representative sampling plans
  - *Laboratory controls [do/did] not include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure components and products conform to appropriate standards of identity, strength, quality and purity. 211.160(b)*

- Stability testing program, including demonstration of stability indicating capability of the test methods
  - *The written testing program designed to assess the stability characteristics of products [do/did] not include:*
    - *The sample size and test intervals for each attribute tested*
    - *Storage conditions for samples retained for testing 211.166*

- Special testing requirements
  - Failure to conduct appropriate laboratory testing for each batch of drug product purporting to be sterile and/or pyrogen-free 211.167(a)

- Adequate reserve samples; documentation of reserve sample examination
  - *An appropriately identified reserve sample(s), of adequate number, representative of each lot or batch of product [is/was] not retained and/or stored under conditions consistent with product labeling and/or in the same immediate container-closure system.*
  - *Reserve samples [are/were] not examined visually at least once a year for evidence of deterioration. 211.170*

- Required testing is performed on the correct samples
  - *In the determination of conformance to appropriate written specifications:*
    - *The samples [are/were] not representative and/or adequately identified for each lot of components 211.160(b)(1)*
    - *The samples [are/were] not representative and/or adequately identified. 211.160(b)(2)*
    - *The samples [are/were] not representative and/or adequately identified for the products. 211.160(b)(3)*

- Laboratory records
  - *[Do/did] not include:*
    - *A statement of each method used in the testing of the sample, indicating the location of data that establishes the methods used in the testing of the sample met proper standards of accuracy and reliability as applied to the product tested. 211.194(a)(2)*
    - *A complete record of all data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays. 211.194*
    - *A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, product container, closure, in- process material, or product, and lot tested. 211.194(a)(4)*
    - *A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors. 211.194(a)(5)*

PART VI - REFERENCES AND PROGRAM CONTACTS

A. REFERENCES:

1. Federal Food, Drug, and Cosmetic Act, and Related Laws.
2. Public Health Service Act.
3. Title 21, Code of Federal Regulations, Parts 11, 210, 211, 314, 600, 601, 606, 607, 610, 640, and 680.
4. Compliance Program Guidance Manual, CP 7356.002, Drug Manufacturer Inspections; CP 7356.002A, Sterile Drug Process Inspections.
5. Guidance on Alternatives to Lot Release for Licensed Biological Products, CBER, July 1993.
6. Guidance to Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product, January 1999.
7. Guideline on General Principles of Process Validation, 1987
8. Compliance Policy Guide (CPG), Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08, Sec 490.100, March 2004.
9. Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Good Manufacturing Practice, September 2004.
10. Guide to Inspections of High Purity Water Systems, ORA/ORO, June 1993.
11. Guide to Inspection of Pharmaceutical Quality Control Laboratories, July 1993.
12. Guide to Inspection of Microbiological Pharmaceutical Quality Control Laboratories, July 1993.
13. Guide to Inspection of Validation of Cleaning Processes, July 1993.
14. Guide to Inspections of Lyophilization of Parenterals, ORA/ORA/DFI, July 1993.
15. Points to Consider in the Manufacture of Recombinant DNA Derived Products, Monoclonal Based In Vitro and In Vivo Products, CBER.
16. United States Pharmacopoeia, Current Revision and Supplements.
17. International Conference on Harmonization Guideline; Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, November 1995.
18. FDA Investigations Operations Manual, Sections 500-529, 560-565, 590-595, 635, 773, 921, 924, 927-928, 1026 and appendix B. http://www.fda.gov/ora/inspect_ref/iom/
19. FDA Regulatory Procedures Manual (RPM), Chapter 4- Advisory Actions, Chapter 5 - Administrative Actions, Chapter 6 - Judicial Actions, Chapter 7- Recall and Emergency Procedures, Chapter 9 - Import Operations/Actions. *http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm*
20. FDA Compliance Policy Guides, Chapter 1- General and Chapter 2 - Biologics. http://www.fda.gov/ora/compliance_ref/cpg/default.htm
21. Glossary of Computerized System and Software Development Terminology, August 1995.
22. Guide to Inspection of Computerized Systems in Drug Processing, February 1983.

B. PROGRAM CONTACTS:

CBER

For questions regarding CBER policy or requests for assistance: OCBQ, HFM-600

1. **Division of Inspections and Surveillance, HFM-650**

   Gilliam B. Conley, Director
   301-827-6220, FAX: 301-827-6748
   Gilliam.Conley@fda.hhs.gov

- **Program Surveillance Branch, HFM-654**

  Janet Ishimoto, Chief
  301-827-6220
  Janet.Ishimoto@fda.hhs.gov

  *Damaris Lopez-Rosario, Team Biologics Liaison
  301-827-6353
  Damaris.Lopez-Rosario@fda.hhs.gov*

- **Biological Product Deviations**

  Sharon O'Callaghan, OCBQ/DIS/PSB, 301-827-6346
  Sharon.Ocallaghan@fda.hhs.gov

  Beth Rogerson, OCBQ/DIS/PSB, 301-827-*6349*
  Susan.Rogerson@fda.hhs.gov

2. **Division of Case Management, HFM-610**

   Diane Alexander, Chief, Biological Drug and Device Compliance Branch
   301-827-6201, FAX 301-594-0940
   Diane.Alexander@fda.hhs.gov

   License Denials, Debarment, Civil Money Penalties, Application Integrity, Biological Product Recalls, **License Suspensions, Revocations and Denials Warning Letters, Seizures, Injunctions, Citations, Prosecutions, Import/Export Programs, Compliance Status Checks, Certificates of Export, Advertising and Promotional Labeling

   Mailing Address for CBER Contacts:

   Food & Drug Administration
   Center for Biologics Evaluation and Research
   Office of Compliance & Biologics Quality
   Division of Inspections and Surveillance, HFM-650
   1401 Rockville Pike
   Suite 200N
   Rockville, MD 20852-1448

3. **CBER Sample Custodian, HFM-*672***

301-594-6517

Center for Biologics Evaluation and Research
Attention: Sample Custodian, HFM-*672*
5516 Nicholson Lane, Building B, Room 113
Kensington, MD 20895

ORA/ORO

For questions regarding inspection policy or requests for guidance, and Core Team contact:

*Lisa Romano, HFC-100, 301-827-3103
Special Assistant to ORO
Lisa.Romano@fda.hhs.gov*

*Ann Marie Montemurro, Supervisor
856-783-1398
Fax 856-783-1513*

Office of Enforcement

For questions pertaining to recalls:

Recall Operations Staff
Division of Compliance Management and Operations, HFC-210
Office of Enforcement
240-632-6856
FAX 240-632-6859

*Armando Zamora
240-632-6855
Armando.Zamora@fda.hhs.gov *

*Cecilia Wolyniak
240-632-6867
Cecilia.wolyniak@fda.hhs.gov

For questions regarding compliance policy issues:

Division of Compliance Management and Operations, HFC-210
240-632-6850
FAX 240-632-6859

Jacqueline Little, *Ph.D.* HFC-210
240-632-6863
OE/DCMO
Jacqueline.little@fda.hhs.gov

PART VII – COORDINATION AND PROGRAM MONITORING

CBER/OCBQ/DIS will work cooperatively with ORA, the Biological Products Field Committee, and the Team Biologics Operations Group to monitor the inspectional and compliance accomplishments under this compliance program, and the status of the inspected industry establishments.

The ORA annual workplan, developed by CBER and ORA, provides overall resource allocations and anticipated numbers of inspections. However, current industry practices encountered during an inspection, the past compliance history of establishments, or other compliance developments, may necessarily result in unplanned inspections or in individual CGMP inspections taking more or less time than estimated in the workplan.

As is customary, ORA continues to have the primary responsibility for ensuring:

1. That the program strategies, priorities, and procedures articulated in this compliance program are followed by the ORA staff, and
2. Potential problems or needs for policy/program clarification are brought to the attention of CBER/OCBQ and the Team Biologics Operations Group.

CBER and ORA jointly coordinate activities to achieve industry compliance with applicable laws, regulations, and Court orders (e.g., Consent Decrees of Permanent Injunction).

CBER/OCBQ will continue to use accomplishment data from the ORA Field Accomplishment and Compliance Tracking System (FACTS), administrative or judicial action recommendations, requests for policy decisions/clarification received from the public or the industry, and input from CBER scientific and product experts to provide overall direction to FDA's CGMP initiatives, which are supported by this risk-based strategic compliance program.

The Team Biologics Operations Group conducts periodic conference calls and/or meetings with participation by ORA and CBER units.

CBER/OCBQ/DIS provides appropriate background material, including license and lot release information, and copies of applicable CBER correspondence and reports, to the Team Biologics investigators prior to scheduled inspections.

CBER/OCBQ will carefully evaluate the experience with this systems-based inspection program through inspection reports and other compliance data to determine its effectiveness and to continually assess and improve the quality of the CBER products inspection program. They also will carefully review industry compliance, product developments within industry, and closely monitor the safety and quality of CBER-regulated biological drug products.

ATTACHMENTS - Product Guidance

ATTACHMENT 1: FRACTIONATORS

Plasma Fractionation

Blood plasma contains a mixture of thousands of different kinds of proteins, only a few of which are of therapeutic interest. To make plasma derivative products, plasma can be treated with a variety of substances to separate the desired proteins from others, in a process called fractionation. Cohn and co-workers at Harvard Medical School developed fractionation of plasma, from pools often derived from thousands of donors, during World War II. Today, most plasma derivative manufacturers use a modified Cohn method developed by Oncley (Cohn-Oncley fractionation process) or further variants of this method, which permit manufacture of additional products.

Fractionation by the Cohn-Oncley method relies on precipitation of plasma proteins by a combination of cold alcohol (usually ethanol)-water mixtures and adjustments of pH, ionic strength, temperature, and protein concentration. Alternatively, some manufacturers separate plasma derivatives by column chromatography using ion exchange, gel filtration, or affinity methods, without alcohol. In all cases, fractions of plasma are separated sequentially, with the product from one step, such as the precipitate and/or supernatant, becoming the starting material for the next step in the fractionation process. If each step is not done properly, subsequent fractions can be adversely affected. Thus, the integrity of each final product is dependent on all of the preceding steps in the process.

Plasma derivatives are similar to other biological products in that they are protein-based and subject to denaturization at high temperatures. These products are usually filled by using aseptic processing techniques, and cannot be terminally sterilized, although in some instances they can be heat-treated in the final container to effect viral inactivation.

Materials System

Source Material

The types of source material used and their suppliers are important. The material should be either licensed Source Plasma or unlicensed Recovered Plasma. Recovered Plasma is a product for which no published standards exist beyond labeling requirements included in 21 CFR 606.121. Licensed manufacturers must provide assurances that plasma for fractionation has been properly processed from the time of collection, and that it does not contain disease-causing agents or contaminants. The plasma for fractionation must be tested and found negative for Anti-HIV-1, Anti-HIV-2, Anti-HCV, HBsAg, and HIVag.

Recovered Plasma can be used if there is a valid short supply agreement in effect with each supplier (see 21 CFR 601.22). The only way in which unlicensed source material may be shipped for use in a licensed product is under short supply. The short supply agreement should include the manufacturer's acceptance criteria for the plasma, e.g., storage/shipping temperatures, viral testing, etc.

Storage of Bulk Fraction

Bulk concentrates should be held and stored in compliance with approved license applications and applicable regulations; see 21 CFR 640.81(d) for Albumin; 21 CFR 640.91(d) for PPF, and 21 CFR 640.102(c) for IG. Many manufacturers store bulk paste below -20 degrees C.

Production System

Pooling

At the minimum, it is recommended that pooling be conducted in an environmentally controlled, but not necessarily classified area (one with some level of particulate control). Manual pooling may take place either in jacketed tanks or in tanks in a temperature controlled area.

Fractionation

Control of the process is essential, since each step yields the starting material for the following steps in the process. Review of the firm's product specific flow diagram(s) may be useful in following the process.

Other areas to consider include; special centrifuges, collection of pastes (precipitates recovered by using centrifugation techniques or filter presses during the fractionation process), filter press operations, filter aid addition, and acetone drying process.

Column Purification

Column chromatography may be used for some plasma derivatives, e.g., coagulation proteins and some immune globulin products. Conditions for collection of active material should be well defined in batch records, and correctly controlled so as to exclude unrelated material.

Column cleaning, rinsing, testing for residuals, and regeneration procedures are very important. Columns not in use should be stored under conditions that inhibit microbial growth and prevent chemical or physical alteration of the medium.

Incubation

Following heat treatment, final containers of Albumin and PPF are incubated at 20-35 degrees C for at least 14 days; see 21 CFR 640.81(g) and 21 CFR 640.91(g).

ATTACHMENT 2: VACCINES

There are many special public health considerations applicable to vaccines and their use. In most cases, vaccines are administered prophylactically, with the intent to stimulate the immune system, and reduce or prevent future occurrence of disease. Vaccines are, therefore, generally administered to healthy individuals, including small children and military personnel. Examples of standard childhood vaccines include; Diphtheria, Tetanus, and Acellular Pertussis; Inactivated Polio Vaccine; Haemophilus influenzae type b; Hepatitis B; and Measles, Mumps, and Rubella. Vaccines may be administered to individuals who have been exposed to a particular infectious agent, in an attempt to prevent the individual from developing the disease. Other vaccines may be administered to alter the course of a non-infectious disease, such as Bacillus Calmette Guerin for the treatment of bladder cancer. Vaccine related products, such as diagnostic skin test antigens, e.g. tuberculin, Coccidiodin, and Histoplasmin, identify persons having an immune response to a particular organism, which may be indicative of an infection.

Many vaccine manufacturers are sole suppliers of specific vaccines or related products.

Facilities and Equipment System

Cross-contamination is a significant concern in facilities that manufacture more than one product. There are specific regulatory requirements aimed at preventing cross-contamination with regard to spore-forming organisms and live vaccines. The regulations, found in 21 CFR 600.10 and 600.11, require that personnel, buildings, and equipment used for processing spore-forming organisms and live vaccines be isolated from other processes, so as to prevent contamination and cross-contamination.

Materials System

Active vaccine components are derived from many sources. A vaccine may be a live attenuated preparation of bacteria, viruses or parasites; inactivated (killed) whole organisms; irradiated cells; crude fractions or purified immunogens (including recombinant DNA derived products); synthetic antigens; or others. A vaccine product may include a combination of the sources described above. Vaccines may also contain adjuvants, which potentiate the immune response to the active component.

Production System

Cell Culture

Includes inoculation of the initial vessel with the starting materials and scale up.

Disruption and Harvest

Disruption (when appropriate) and harvesting of the product is performed using chemical, physical, or enzymatic means. All process parameters should be specified and documented in the batch production records.

Adventitious Agent Removal

For products derived from cells of human or animal origin, viral removal must be performed in accordance with the process described in the approved license application. In some manufacturing operations there may be a specific viral removal step. In other operations, viral removal may be accomplished by a step or series of steps in the manufacturing process, which are not specifically considered to be for viral removal, e.g., chromatography.

Purification

Purification of vaccine bulks may include one or more of the following methods:

- Column or batch chromatography
- Centrifugation
- Filtration
- Precipitation followed by filtration or centrifugation

Adsorption

Adsorption is the process of adding an aluminum adjuvant to a vaccine antigen in order to increase its immunogenicity. Aluminum adjuvants of various formulations are used in vaccine production. The vaccine manufacturer should specify the quality attributes of the adjuvant, including percent purity, particle size, and protein binding capacity. Quality attributes are generally specified on Certificates of Analysis (COA) provided by the adjuvant manufacturer. Batch records must specify the type of adjuvant used.

Aluminum adsorption may be performed on intermediates, bulks, or both. Two general procedures are used for aluminum adsorption: (1) addition of pre-formed aluminum adjuvant to vaccine antigens, and (2) on-site formulation of an aluminum adjuvant. For some vaccines, conditions for binding the aluminum adjuvant to the antigen may be known, and specifications will be established for this process. However, for many products, the scientific mechanism for binding the aluminum adjuvant to the antigen has not been determined, and therefore, no binding specifications will be established.

The extent of adsorption of an aluminum adjuvant to an antigen may be affected by production process parameters such as pH, phosphate concentration, and adequate mixing. These adsorption process parameters should be specified by the manufacture, in order to promote consistency in manufacturing.

Note: Products containing aluminum adjuvant are formulated aseptically because once they are alum adsorbed they cannot be sterile-filtered.

Inactivation

If the active ingredient of the vaccine is a killed or inactivated version of a live bacteria or virus, the methods for inactivation will have been established by the manufacturer and reviewed during product approval. Either heat or chemical treatment may be used for inactivation. All process parameters should be monitored and appropriate testing performed to demonstrate inactivation. Appropriate containment procedures should be established for the agent being inactivated.

If the active ingredient of the vaccine is a bacterial toxin, methods of toxin inactivation will also have been established by the manufacturer and reviewed during product approval. Treatment

with formaldehyde is an example of toxin inactivation. All process parameters should be monitored, and appropriate testing performed to demonstrate inactivation of the toxin.

Conjugation

The chemical linkage of a polysaccharide immunogens to a carrier protein generally forms conjugate vaccines. Polysaccharide immunogens are extracted from bacterial cells. Carrier proteins are usually derived from bacterial cells that are different from those used to produce the polysaccharide. The polysaccharide immunogens and the carrier proteins are purified using a variety of methods including; centrifugation, buffer exchange, diafiltration, and chromatography. The purification process should be monitored through in process testing in order to assure the purity of the polysaccharide and carrier protein, and to assure removal of product and process related impurities. Specifications for in-process testing should be specified and results documented in the batch production records.

After purification of the polysaccharide and carrier protein, a chemical reaction(s) is (are) used to covalently link the two molecules together. The reaction should be monitored in order to determine completion of the conjugation reaction, amount of impurities, yield, and purity of the final conjugate product. Additional purification steps may be employed to remove excess reagents and reaction by-products. In addition, post-purification steps may be performed to produce a stabilized conjugate.

Endotoxin Levels

Some bacterial vaccines are manufactured from gram-negative organisms, which produce endotoxin. In these types of vaccines, the endotoxin is often the immunizing agent of interest, and the manufacturer will have defined specifications for endotoxin levels in the final product. The production and testing records should be routinely reviewed to assure that the final product meets the pre-defined endotoxin specifications.

Finished Products

For vaccines and related products, the biological drug substance may be diluted, adsorbed with adjuvant, mixed with stabilizers, mixed with preservative, and/or lyophilized to become the final finished product. In addition, more than one vaccine can be formulated together to produce a combination vaccine product. There are several different final container/ closure systems for vaccine products. Examples include capsules (blister packed), sachets, oral solutions, sealed glass ampules, single-dose syringes, single-dose and multi-dose vials (solutions or lyophilized), and multiple puncture devices pre-loaded with antigen.

ATTACHMENT 3: RECOMBINANT PRODUCTS

While the specifics of each manufacturing operation may be different, the manufacture of recombinant biological drug products has a number of common elements. The process usually begins with a master cell bank (MCB), which is derived from a single cell or colony, and is stored to assure genetic stability. The MCB provides source material for the working cell bank (WCB), which is used to initiate the production batch.

One method of propagating sufficient cells to manufacture product is through fermentation. Fermentation is the process of multiplying the cells from the WCB into a quantity sufficient to extract the desired product. Cells from the WCB are inoculated into a medium to begin fermentation.

After a number of passages in small vessels (usually flasks), the inoculated medium is added to a fermentation vessel, usually a bioreactor. At the conclusion of the fermentation process, the cells are subjected to a variety of purification steps, which are designed to remove extraneous cellular material and/or media components, and inactivate or remove any adventitious agents.

Purification can include filtration, chromatography, extraction, and enzyme digestion. The resulting final bulk product may be filled in this form, further diluted and filled, or lyophilized before filling.

Components

Master Cell Bank (MCB) and Working Cell Bank (WCB)

i. Storage Conditions

The manufacturer should clearly define storage conditions for the MCB and WCB, and have a system in place to ensure that the storage conditions are maintained. If the storage requirements specify a temperature limitation, there should be documentation of routine temperature readings, and a working alarm system in place in case the temperature deviates from the established one.

ii. Identification

There should be documentation that the WCB was characterized and met specifications before use. If any WCB that did not meet specifications was used, determine which lot(s) of product was manufactured from the WCB and the disposition of the product.

The firm should have records to show the origin and history (number of passages) of the MCB and WCB.

iii. Handling of the WCB

Review the records for inventory and handling of the WCB and ensure they are adequate to protect the integrity of the cells. Verify the firm has records to show which WCB is used to initiate a production batch.

iv. New MCB

The firm must have an approved license application or submit a supplement to its license before generating a new MCB from a WCB. The firm should also have records documenting that the new MCB was tested and properly characterized.

Endotoxins

Production should be performed in a controlled environment that prevents an increase in the product's microbial load beyond its design specifications. Procedures to prevent equipment or product contamination by any substance that could reasonably be expected to have an adverse effect on product quality should be in place and followed. Precautions should be taken to prevent contamination or cross-contamination in areas for the preparation of cell banks. Product manufacturing processes capable of promoting microbiological growth should be monitored for bioburden on a routine basis.

Fermentation/Bioreactors

The fermentation process includes inoculation of the initial vessel with the WCB and scale-up. Often the early passages are conducted in open vessels under laminar flow. The larger vessels are generally closed systems. If the system is closed, there should be no breaks in the system. All steps in the process should be recorded in the batch record.

Disruption and Harvest

Disruption (when appropriate) and harvesting of the product is performed using chemical, physical, or enzymatic means. All essential parameters should be documented.

Purification

Purification is generally performed using a combination of column chromatography, filtration and centrifugation. The method being used should be the same as the approved process and all steps should be documented in the batch record.

ATTACHMENT 4: ALLERGENICS

Under the Public Health Service Act (PHS Act), CBER licenses allergenic products that are used for the diagnosis and treatment of individuals with sensitivity to various materials. Allergenic products are biological products that are administered to man for the diagnosis, prevention, or treatment of allergies. The products are manufactured from source materials that may include pollen, insects, mold, food and animals.

In addition to meeting the definition of a biological product, allergenic products also fall within the definition of a drug as found in Section 201(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Consequently, these products are regulated and inspected by authorities delegated under the PHS Act, the FD&C Act, and other authorities, including the applicable sections of the Biologics regulations (21 CFR Parts 600-680) and the Drug regulations (especially Parts 210 and 211, Current Good Manufacturing Practice).

Allergenics include injectable products, and allergen test patches. This program is not intended to address allergen test patches. Injectable products are provided to the practitioner as either ready to use (glycerinated, aqueous, or alum-bound) or as a lyophilized product plus diluent. If the product is supplied as a lyophilized product, the diluent is considered a component of the product. Injectable products are required to be sterile.

Standardized and Non-standardized

The FDA has determined that a number of allergenic products must be in a standardized form. Standardized allergens must be tested for safety, sterility, potency and identity, and stability. Standardized allergens are also subject to CBER lot release. Non-standardized allergens should be tested for safety and sterility. Exceptions to the testing required in 21 CFR 610.11 and 610.12 are found in 21 CFR 680.3(b) and (c).

Prescription Sets

The composition of prescription sets is generally considered to be the pharmacy practice (regulated by State authorities), and as such, is not subject to this program. However, investigators should confirm that the facility has a valid prescription on file for each set, and that the bulk or stock materials were manufactured in accordance with CGMPs. Prescription sets are manufactured from bulk or (licensed) stock concentrates in accordance with an individual physician's prescription.

Materials System

Source Material

The source material contains the active substance, which is responsible for the allergic response. Source materials and source material manufacturers are not required to register or list, and are not licensed. These materials are not finished biological drug products, so manufacturers are not held to the requirements in Part 211.

Source material suppliers are subject to the requirements in 21 CFR Parts 600-680. Specific criteria for source materials can be found in 21 CFR 680.1(b) and (c). Because source materials

are components of a biological drug, they must be manufactured in accordance with the general principles of CGMPs.

Most finished product manufacturers obtain their source materials from source material suppliers. If the finished product manufacturer manufactures its own source materials, the source material manufacturing operations should be inspected, if it is within the same facility or a facility in close proximity to the finished manufacturing site.

Per 21 CFR 680.1(c), allergenic product manufacturers must list with CBER the name and address of each source material supplier. The list must be updated annually. The source material suppliers should be the same as those reported to CBER.

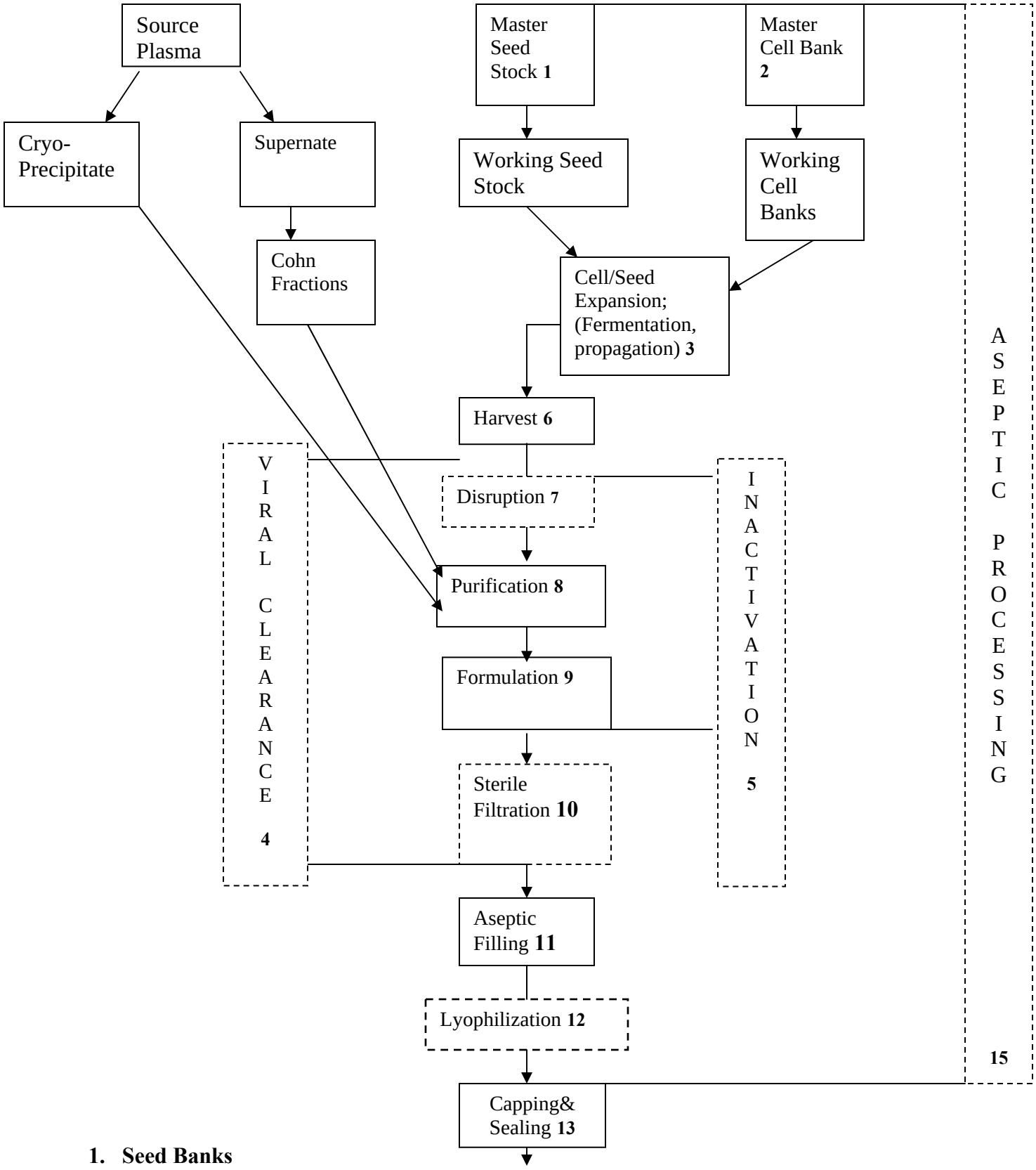
Animal Source Materials

Animals of the equine genus are treated to maintain immunity to tetanus and reports of any diseases in 680.1(b)(3)(iv) should be reported to CBER as required.

ATTACHMENT 5: FLOW DIAGRAM AND APPENDICES

Fractionated Plasma Products
Attachment 1

Vaccine and Recombinant Product
Attachments 2 and 3



1. Seed Banks

Master Viral Seed (MVS) and Working Viral Seed(s) (WVS)

By definition, a WVS consists of material having the same composition and origin, with a specific lot number and date of manufacture, and, in many cases, is one passage removed from the MVS. The MVS, and at least one WVS, should be qualified for use during the licensing process. The firm should have a complete history for the MVS and the WVS, including the passage history and testing profiles for each. The storage and handling of the viral seeds and the use of WVS in vaccine manufacture are extremely important. Batch records should clearly indicate the WVS used.

New Viral Seed

A new MVS for a licensed product requires a CBER approved supplement prior to release of any vaccine derived from the new MVS. A new WVS must be reported to CBER, either as a prior approval supplement, CBE-30, or, with appropriate documentation, in the annual report. If the manufacturer has changed either the MVS or WVS since licensing or the previous inspection, the change should be reported to CBER in the appropriate manner. If a new viral seed was produced, there should be records describing the production of the new viral seed to assure that the viral seed was produced without deviations from the appropriate regulations and license requirements.

Storage

Maintenance of the MVS and the WVS under tight security is necessary, inasmuch as these items are an integral part of the production process. The viral seeds should be stored separately, in multiple locations, at the appropriate temperature, with adequate controls to prevent unauthorized access and loss of material due to equipment failure. The storage conditions, including temperature, should be clearly defined, validated, and documented. A working alarm system for each storage location is frequently seen.

Inventory

The firm must maintain an accurate inventory of all viral seed stocks, and each sample of viral seed must be clearly marked to indicate its contents. The inventory records should correlate to the amount of material on hand. The firm should maintain adequate control of WVS samples destined for use in production in order to assure protection of the samples and personnel safety.

Suitability of the WVS

The manufacturer should be able to provide data (e.g., titer, sterility) supporting the continued suitability of the current WVS for use in manufacture.

Bacterial Primary seeds and Secondary (Working) seeds Storage conditions

Maintenance of both the primary and the working seeds under tight security is necessary, as they are an integral part of the production process. Bacterial primary seeds should be stored separately, in multiple locations, at an appropriate temperature, with adequate controls to prevent unauthorized access and loss of material due to equipment failure. The storage conditions, including temperature, for the primary and secondary seeds should be clearly defined and documented. A working alarm system for each storage location is frequently seen.

Identification

The history and characteristics of each bacterial strain used in the manufacture of a product should be maintained. Characterization may include origin of the isolate, speciation, serotyping, biochemical testing, virulence, genetic characterization, and in-vivo animal or human testing. The primary and secondary seeds should meet specifications prior to use in production and appropriate records of characterization should be maintained. The manufacturer should have records to demonstrate which secondary seed lot is used to initiate a production batch.

Seed Integrity and Passage Limitation

In order to maintain genetic stability of the bacterial strain, the number of passages permitted for primary and secondary seeds are limited. The number of passages should be specified in an appropriate SOP based on the number of passages approved in the license application. Lot number and date of preparation should identify primary and secondary seed lots. Periodic tests should be performed in order to verify the integrity of the strain characteristics and freedom from contamination with extraneous organisms. Appropriate records should be maintained detailing the number of passages of each primary and secondary seed, and all tests performed to demonstrate strain integrity and freedom from contamination.

New Primary and Secondary Seeds

A change in a primary seed requires submission and approval of a supplement (prior approval supplement or PAS) prior to use of the primary seed in production. Establishment of new secondary seeds from a previously approved primary seed may be submitted to CBER as a CBE-30 supplement or in an annual report, provided that the change is made according to an SOP in the approved license application, unless otherwise specified.

2. Cell Banks

Master Cell Bank (MCB) and Working Cell Bank (WCB)

Cell bank systems are used for storage of some cell lines that are used as hosts for viral propagation. Both the MCB and WCB are qualified for manufacture during the licensing process. In most instances, a MCB is more extensively characterized than the WCB, although a manufacturer can be licensed for a product where the WCB is more extensively characterized than the MCB. In the latter case, the following comments for a MCB would be applied to the manufacturer's WCB.

Storage Conditions

The storage conditions for the MCB and WCB should be clearly defined. The MCB should be stored in more than one location, in the event that the MCB stored in one location is destroyed. Personnel access to both the MCB and WCB should be clearly specified and tightly controlled. Maintenance of the storage conditions should be assured. Storage requirements specifying temperature limitations, should document conditions and a working alarm system should be in place for temperature deviations from the established limits.

Identification

The cell bank should be well-characterized, and meet specifications prior to use in production. Any new WCB should be reported to CBER in the appropriate manner. If an approved procedure is in place, production of a new WCB according to the approved procedure may represent a minor change to be included in the annual report of minor manufacturing changes. A cell bank that did not meet specifications should not be used. In the event this did occur there should be a record of an investigation, which includes a determination of how it happened, and the disposition of the lot(s) manufactured from the cell bank. The number of passages or doublings of a cell bank is controlled in order to assure genetic stability and, for attenuated vaccines, freedom from virulence. The number of permissible passages or doublings is product specific and will be specified in the firm's approved license application. The firm should have records identifying the passages and/or doublings of the MCB and WCB according to the procedures specified in the approved license application.

Handling of the Cell Bank

Storage, inventory, and handling of the MCB and the WCB should be adequate to protect the integrity of the cells with documentation to support. The firm should maintain records identifying the cell bank used to initiate a production batch and, if diploid cells are used for production, that the cells were utilized at the appropriate passage levels, as specified in the license.

Viral Safety Evaluation of Cell Banks

Because cell lines are derived from human or animal hosts, viral safety testing is often required in order to assure that the cell lines are free from contaminating viral agents. Viral contaminants may originate from the host cell itself (endogenous), or may be introduced into the cell line during production (non-endogenous).

Tests performed on the MCB or WCB to demonstrate the absence of adventitious agents are specified in the license application or approved supplements. For some products, each batch of production cells is also tested for possible viral contaminants that may have arisen during production.

New MCB and WCB

Establishment of a new MCB requires a license application or prior approval supplement. Establishment of a new WCB from a previously approved MCB may be reported in an annual report, provided that the WCB was generated in accordance with an SOP on file in an approved license application. A new WCB should be from an approved MCB. The testing of the new WCB should be performed in accordance with the SOP in the approved application or as submitted in a prior approval supplement.

3. Cell/Seed Expansion

Cell Culture

The process includes inoculation of the initial vessel with the starting materials and scale-up. Often the early passages are conducted in open vessels under laminar flow. The larger vessels are generally closed systems. There should be no breaks in connections between processing vessels in a closed system.

Fermentation/Bioreactors

The fermentation process includes inoculation of the initial vessel with the WCB and scale-up. Often the early passages are conducted in open vessels under laminar flow. The larger vessels are generally closed systems. There should be no breaks in connections between processing vessels in a closed system.

4. Viral Clearance

Products derived from cells or source material of human or animal origin, viral inactivation/removal should be performed in accordance with the process in the approved license application. In some manufacturing operations, there will be a specific viral inactivation/removal step; in other operations, viral inactivation/removal will be accomplished by a step or steps in the manufacturing process that are not specifically considered to be viral inactivation/removal steps. In some instances more than one viral clearance step is used for a given product.

There should be complete segregation of pre-and post-viral inactivation/removal steps (with the exception of products such as Albumin, which are virally inactivated in final containers). Separate areas with a dedicated air handling unit or single pass air should be used for those steps that occur after viral clearance procedures.

Heat treatment is one method of clearing infectious agents from biologicals. Heat treatment is sometimes referred to as pasteurization, and heating equipment such as large water baths, may be referred to as pasteurizers. Technically, however, pasteurization is heating at 63 degrees C for 30 minutes, which is not sufficient to render plasma derivatives virally inactive.

The parameters specified in the batch record should be achieved such that the validated process for viral inactivation/removal is accomplished. Changes made to the process, which do not require submission of a supplement to CBER, should be validated.

5. Inactivation

If the active ingredient is a killed or inactivated version of a live bacteria or virus, the methods for inactivation will have been established and reviewed during product approval. Either heat or chemical treatment may be used for inactivation. The manufacturer should have validated the process and followed the validated procedures during production. All parameters should be monitored and the appropriate testing is performed with acceptable results. The containment procedures should be adequate for the agent being inactivated. If the active ingredient is a bacterial toxin, methods of toxin inactivation will also have been established and reviewed during product approval. Treatment with formaldehyde is an example of toxin inactivation. As stated above the manufacturer should follow validated procedures for toxin inactivation, perform appropriate testing to demonstrate inactivation of the toxin, and obtain test results that are within the specifications approved in the license.

6. - 7. Disruption and Harvest

Disruption (when appropriate) and harvesting of the product is accomplished using chemical, physical, or enzymatic means. The firm should only be using their approved method(s) and all essential parameters should be documented.

8. Purification

Purification is generally performed using a combination of column chromatography, filtration and centrifugation. The method being used should be the same as the approved process and all steps should be documented in the batch record.

8a) Column or Batch Chromatography

Column or batch chromatography may be used for the purification of plasma derivatives, bacterial, viral and recombinant products. Conditions for collection of active material should be well defined in batch records and correctly controlled so as to exclude unwanted material. Transfers should be made in an environmentally controlled system.

Column cleaning, rinsing, testing for process residuals, leaching from column media, and regeneration procedures are very important. These procedures must be validated and followed. There must be a defined and validated number of times a column may be re-used, and this limit must be followed.

Validation of production scale columns must be performed. This validation may be performed concurrently, and may be in progress. Columns not in use must be stored under conditions that inhibit microbial growth and prevent chemical or physical alteration of the medium. A system must be in place to monitor column performance, so that if the column begins to degrade or perform outside the validated parameters, it can be immediately replaced or regenerated, as specified by appropriate SOPs, and supported by process validation. Column support equipment such as UV monitors, pumps, chart recorders, PLCs, etc., should have appropriate installation qualification (IQ), and operational qualification (OQ). These should also be included in routine calibration schedules. Firms should document calibration, maintenance, replacement, and upgrades; these operations should be performed in accordance with SOPs.

8b) Centrifugation

Low-speed, high-speed, ultra-centrifugation or continuous flow centrifugation methods are commonly used in harvest and purification schemes. Centrifuge run time and speed (rpm), specific equipment number (if more than one option), and rotor used should be documented in the batch production record. Centrifuges should have appropriate equipment validation, IQ, OQ and performance qualification (PQ), and should be re-certified/calibrated on a regular basis to assure that the specified time and rpm produces the desired relative centrifugal force (rcf), to achieve adequate separation. Routine maintenance should include examining the rotors for wear. Rotors should be dedicated to the product or have a validated cleaning procedure. The centrifuge rotors as well as the inside of the centrifuge should have a validated cleaning process, as this technique commonly produces aerosols. The centrifugation step should have been included in the overall process validation, so that the stated time and speed reliably produce the desired separation. Any changes in the centrifugation equipment (new rotors, and especially a new centrifuge) should be in accordance with SOPs and documented. For example, 3200 rpm at 20 minutes in one brand of a centrifuge may not achieve the same rcf as the same time and speed in a similar-looking instrument from another manufacturer.

8c) Filtration

There are various types of filtration methods, such as diafiltration, ultrafiltration and microfiltration that may be used in the purification of vaccine products. Some of the filters used may be single-use and some may be multi-use. The filters are usually placed within a filter housing apparatus. The criteria used for the evaluation of the column purification should also be applied to the filter housings and the multi-use filters.

8d) Precipitation followed by Filtration or Centrifugation

Conditions for precipitation (time, temperature, concentration, etc.) should be based on process validation and be defined in the batch production record. Previous comments regarding filtration and centrifugation apply, as appropriate.

9. Formulation, Filling, and Packaging

For some biological drug products, the drug substance may be diluted, adsorbed with adjuvant, mixed with stabilizers, mixed with preservative, and/or lyophilized to become the final biological drug product. In addition, more than one component can be formulated together to produce a combination vaccine product.

10. Filtration

The sterilizing filters should be validated for product compatibility and microbial retention and that they are adequate for their intended use. The filters should be evaluated prior to use to determine if they meet specifications. Integrity testing should be performed on filters post-fill and results should be in keeping with the manufacturer's validated specifications. Some bulk products are held after sterile filtration prior to filling. The holding period and storage conditions should be validated.

11. Filling

If the duration of filling is lengthy, time limits should be established and validated to ensure that the duration of the fill does not affect the potency of the product and its susceptibility to microbial contamination. An SOP should be in place for interruptions in the fill, should it occur. Some products are held after sterile filtration prior to filling. The holding period and storage conditions should be validated. Filling lines should be inspected to ensure that carryover does not occur from previous fills.

12. Lyophilization

Loading of the lyophilizer should be done either under Class 100 (ISO 5) conditions, or as otherwise approved by CBER. The lyophilization process must be performed in accordance with validated parameters, including the placement of products in the lyophilizer.

If the vials are overlaid with gas (usually nitrogen) the firm's procedures for integrity testing of sterilizing filters, sterilization, and replacement, should be documented and followed.

13. Containers/Closures

There are several different final container and closure systems for biological drug products. Examples include capsules (blister packed), sachets, oral solutions, sealed glass ampules, single-dose syringes, single-dose and multi-dose vials (solutions or lyophilized), and multiple puncture devices pre-loaded with antigen. The firm should have adequate written specifications and procedures describing the receipt, handling, sampling, and storage of containers and closures, especially those that need to be sterile and/or pyrogen-free.

The firm should have procedures and controls used to verify and assure suitability of containers and closures, for accepting/rejecting final product containers and closures from the vendor, a validated container/closure system(s) and for the reconciliation of final containers.

The depyrogenation and sterilization procedures for product containers, closures, and components should be appropriately validated, and followed. Equipment used for these processes (stopper processors, tunnel sterilizers, ovens, autoclaves) should be properly maintained and re-qualified periodically.

14. Labeling/Packaging

Applicable labeling requirements are found in 21 CFR 201, as well as various sections of Parts 610 and 660. Specific wording for labeling is reviewed and approved by CBER. Products should be labeled as approved by CBER.

Process controls during labeling and packaging, such as inspection, label security, and label accountability, should be written and followed. Visual inspection should be performed in appropriate areas, and operators should be trained and certified in visual inspection procedures.

15. Aseptic/Controlled Process:

Biological products are manufactured in a controlled environment. The entire process does not have to be performed under aseptic conditions, but the firm should have established the point in the process where aseptic controls begin. Products should be maintained in a controlled environment throughout the process and have specified in-process bioburden action and alert limits for which the firm can provide a meaningful rationale.

a. *Aseptic processing from early manufacturing steps:*

Some products undergo aseptic processing at some or all manufacturing steps preceding the final product closing step. With some products, there is a point in the process after which a product can no longer be rendered sterile by filtration. In such cases, the product should be handled aseptically at all steps subsequent to filter sterilization. In other instances, the final biological drug product cannot be filter sterilized, and, therefore, each component in the formulation should be rendered sterile and mixed aseptically. For example: products containing aluminum adjuvant are formulated aseptically because once they are alum adsorbed, they cannot be sterile-filtered.

When a product is processed aseptically from the early stages, the product and all components or other additions are rendered sterile prior to entering the manufacturing process. It is critical that all transfers, transports, and storage stages be carefully controlled at each step of the process to maintain sterility of the product.

Procedures (e.g., aseptic connection) that expose a product or product contact surfaces must be performed under unidirectional airflow in a Class 100 (ISO 5) environment. The environment of the room surrounding the Class 100 (ISO 5) environment must be Class 10,000 (ISO 7) or better. Microbiological and airborne particle monitoring should be performed during operations.

Microbial surface monitoring should be performed at the end of operations, but prior to cleaning. Personnel monitoring should be performed in association with operations.

Process simulation studies should be designed to incorporate all conditions, product manipulations, and interventions that could impact on the sterility of the product during manufacturing. The process simulation, from the early process steps, should demonstrate that process controls are adequate to protect the product during manufacturing.

These studies should incorporate all product manipulations, additions, and procedures involving exposure of product contact surfaces to the environment. The studies should include worst-case conditions such as maximum duration of open operations and maximum number of participating operators. Process simulations do not need to mimic total manufacturing time if the manipulations that occur during manufacturing are adequately represented.

It is important that process simulations incorporate storage of product or transport to other manufacturing areas. For instance, there should be assurance of bulk vessel integrity for specified holding times. The transport of bulk tanks or other containers should be simulated as part of the media fill. Process simulation studies for the formulation stage should be performed at least twice per year.

For lyophilization operations, unsealed containers should be exposed to pressurization and partial evacuation of the chamber in a manner that simulates the process. Vials should not be frozen, as this may inhibit the growth of microorganisms.

b. *Aseptic processing of cell-based therapy products (or of products intended for use as cell based therapies)*

Cell-based therapy products represent a subset of the products for which aseptic manipulations are used throughout the process. Where possible, closed systems are used during manufacturing. Cell-based therapy products often have short processing times at each manufacturing stage, even for the final product. Often, these products are administered to patients before final product sterility testing results are available. In situations where results of final sterility testing are not available before the product is administered, additional controls and testing could be instituted. For example, additional sterility tests can be performed at intermediate stages of manufacture, especially after the last manipulation of the product prior to administration. Other tests that may indicate microbial contamination, such as microscopic examination, gram stains, and endotoxin testing should be performed prior to product release.

c. *Manufacturing and aseptic processing*

The manufacturer must meet their established microbial specifications for in process testing for the lots made. Observation of the aseptic processes should be made, when possible, to evaluate aseptic technique. All connections and transfers to manufacturing should be made in an aseptic manner.

An SOP should be in place for interruption of the fill, should it occur. Some bulk products are held after sterile filtration prior to filling. The holding period and storage conditions should have been validated. Procedures should be in place for limiting access to controlled and classified areas.

Filters should be evaluated prior to use to assure they meet specifications. Integrity testing should be performed on filters post-fill and results should be in keeping with manufacturers and validated specifications.

Cleaning and sanitization procedures for the aseptic core should be written and followed. These procedures should employ cleaning agents according to results of validation studies and surfaces should be monitored to demonstrate continued efficacy. For lengthy filling operations, time limits should be set and validated to assure that the duration of the fill does not affect the potency of the product and its susceptibility to microbial contamination.

There should be a program(s) in place for training operators. In addition to training in the manufacturing process, the operators should also be trained in proper gowning technique. Written procedures for gowning should be in place and followed.

The firm's aseptic processing areas (filling and lyophilization) should be designed using 21 CFR 211.42(c)(10), the Guideline on Sterile Drug Products Produced by Aseptic Processing, and the Draft Guidance for Industry – Sterile Drug Product Produced by Aseptic Processing – Current Good Manufacturing Practices as guides.

Class 100 (ISO 5) conditions must be validated and maintained in areas in which sterile product and components, including container/closure systems, are exposed. Monitoring critical and immediately surrounding clean areas as well as personnel should include routine identification of microorganisms to the species level.