

CHAPTER 56 -- DRUG QUALITY ASSURANCE

| | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------|
| SUBJECT: Inspections of Licensed Biological Therapeutic Drug Products | | IMPLEMENTATION DATE October 20, 2003 |
| *Revision note: This program is being reissued as a CDER program due to the transfer of certain biological products to CDER's jurisdiction effective FY04. This reissued program retains most of the instructions and procedures from the prior version published by CBER: 7341.001 . (CBER may continue this same program under their program number (7341.001) for products remaining under their jurisdiction.) Products regulated as human drugs by CDER prior to the transfer of certain biological products from CBER are subject to the existing Compliance Program for these products, 7356.002 , only.* | | COMPLETION DATE September 30, 2006 |
| DATA REPORTING | | |
| PRODUCT CODES | PRODUCT/ASSIGNMENT CODES | |
| 57YY- | 56002M GMP Inspections 46832M Pre-license Inspections | |

FIELD REPORTING REQUIREMENTS:

Domestic Inspections: A copy of each establishment inspection report (EIR), including endorsement and classification, should be submitted to *CDER, Office of Compliance Division of Manufacturing and Product Quality (DMPQ), Investigations & Preapproval Compliance Branch (HFD-322).* Exhibits should not be included unless specifically requested. A copy of the coversheet and endorsement should be sent to HFC-100. The complete original report, including exhibits, should be sent to the home district for filing.

Foreign Inspections: The complete original EIR, including exhibits, should be forwarded to *CDER Division of Manufacturing and Product Quality (DMPQ), Investigations & Preapproval Compliance Branch, Foreign Inspection Team (FIT), HFD-325, regardless of classification.* A copy of the coversheet and endorsement should be sent to HFC-100.

PART I - BACKGROUND

FDA is responsible for ensuring that biological products are safe and effective and in compliance with the law and FDA regulations. Biological products are licensed under the provisions of Section 351 of the Public Health Service Act (42 USC) (PHS Act).

Licensed therapeutic products are regulated under both the Federal Food, Drug and Cosmetic Act (FD&C Act) and the PHS Act. For those therapeutic products that meet the definition of a drug under the FD&C Act, the manufacture of these products must be performed in accordance with the cGMP regulations in 21 CFR Parts 210 and 211. As the products are also biologicals, manufacturers must also comply with the applicable regulations in 21 CFR Parts 600-680.

Technical advances over the last 15 years have greatly increased the ability of manufacturers to control and analyze the manufacture of many biotechnology-derived therapeutic products. Specified biotechnology-derived products, defined in 21 CFR 601.2, are exempted from complying with certain biologics regulations and are not required to be submitted for lot release. These products are (1) therapeutic synthetic peptides of 40 or fewer amino acids; (2) therapeutic DNA plasmid products; (3) monoclonal antibodies for in vivo use; and (4) therapeutic recombinant DNA-derived products.

This program covers both specified and non-specified therapeutic biological drug products now regulated by CDER, but formerly regulated by CBER under this same program.

Technology

While the specifics of each manufacturing operation may be different, the manufacture of therapeutic biological products has a number of common elements. The processes usually begin 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 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 subject to a variety of purification steps, 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.

Team Biologics

In October 1998, responsibility for conducting biennial inspections of therapeutic product manufacturers was transferred to the ORA Team Biologics/Core Team. The Core Team will also be primarily responsible for handling any enforcement actions that result from inspections performed under this program, in accordance with the procedures set forth in the Team Biologics case processing procedure.

The Core Team will ensure that the home district is advised of activities related to facilities in their areas and may solicit assistance from the home district in carrying out the inspections or enforcement activities.

Pre-license inspections are the responsibility *of CDER*, and will include a field investigator whenever possible.

PART II - IMPLEMENTATION

A. Objectives

This program has the following objectives:

- To ensure the safety and effectiveness of licensed biological therapeutic drug products by determining that they are manufactured in compliance with current Good Manufacturing Practice regulations and that they comply with standards and commitments made in license applications and/or supplements.
- To encourage voluntary compliance by identifying practices, which need correction or improvement, and to identify areas in which firms need to establish and implement programs.
- To provide regulatory/administrative guidance to ensure that appropriate enforcement actions are initiated against those manufacturers found to be in significant noncompliance with applicable laws and regulations.
- To provide information and guidance to investigators assigned to perform biennial GMP or for cause inspections of manufacturers of licensed biological therapeutic drug products.

B. Program Management Instructions

Firms covered under this program include all licensed manufacturers of biological therapeutic drug products, including biotechnology-derived products.

Work planning for these inspections will be coordinated by Team Biologics. Each facility and its biological products are to be covered in a single, comprehensive inspection that assesses the adequacy of all-significant processes and systems. The inspections should be performed on at least a biennial basis, or more often if circumstances, such as the firm's compliance history, so warrant.

The inspections will be conducted using a team approach whenever possible, with an ORA Team Biologics/Core Team investigator leading and a *CDER* product reviewer participating. The inspection team may include other ORA or *CDER* members, as necessary, to assure appropriate coverage of the facility. If *CDER* on-site participation is not possible, the Core Team will proceed with the inspection with other ORA members, as necessary.

Historically, there have been individual inspections for each therapeutic class. At some firms, this has resulted in a burdensome number of redundant inspections. This program departs from this practice, in that there will be one inspection of a facility to cover all products. If a company makes products reviewed by multiple divisions in *CDER*, the Center may send individuals from each division, but they should try to stagger the attendance of the additional persons to keep the number of individuals at the firm at one time to a reasonable level.

PART III – Inspectional

Every effort should be made to inspect each licensed firm at least once every two years or more frequently if the firm's compliance history so warrants.

A. Inspectional Procedures

Review and use applicable sections of Compliance Program 7356.002, Drug Manufacturing Inspections; Compliance Program 7356.002A, Sterile Drug Process Inspections; and Biotechnology Inspection Guide. If there are differences between the instructions in this program and the above referenced documents, investigators should follow the instructions in this program when conducting inspections of manufacturers of licensed biological therapeutic products.

Manufacturers of licensed biological therapeutic drug products are subject to the regulations in 21 CFR Parts 600-680 and Parts 210 and 211. Manufacturers of licensed products must also conform to the conditions in their approved license applications and supplements. If it is necessary to verify the content of a license application or supplement, contact CDER for assistance.

B. Inspection

1. Components

Manufacturers who purchase components from outside sources are required to establish adequate quality requirements and specifications for such components. The licensed manufacturer is ultimately responsible for ensuring that components 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. Validity of the certificates should be established by the manufacturer through experience, historical data, testing, and/or audits of the supplier.

For components received from outside sources, either purchased or otherwise received, verify that:

- The firm has written, approved, specified requirements for the component(s);
- The firm evaluates and selects suppliers based on their ability to meet specified requirements; and
- 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 ensure that 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) as described in a license application are performed. If the license application includes certification supporting freedom of substances from adventitious agents, this should be confirmed during inspections.

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.

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

i. Storage conditions

The storage conditions for the MCB and WCB should be clearly defined. Ensure that the storage conditions have been maintained. If the storage requirements specify temperature limitations, ensure that there is documentation of the temperature and determine if there is a working alarm system in place if the temperature deviates from the established one.

ii. Identification

Ensure that the WCB has been 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.

Ensure the firm has 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. Ensure the firm has records to show which WCB is used to initiate a production batch.

iv. New MCB

If the firm has generated a new MCB from a WCB, ensure that there is an approved license application or supplement for this. Ensure that the new MCB is tested and properly characterized.

b. 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 holding times and conditions, validated the holding times and conditions, and has records to show the conditions are met.

c. Containers/closures

Ensure that 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.

Review procedures for accepting/rejecting final product containers and closures from the vendor. Determine whether the firm conducts vendor audits and, if so, how and with what frequency.

Review the procedures and controls used by the firm to verify and ensure suitability of containers and closures. Evaluate procedures used by the firm to validate the container/closure systems. Report any changes in container/closure systems that have not been validated.

Review SOPs for reconciliation of final containers.

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

2. Manufacturing

a. Aseptic/controlled process

Therapeutic products are manufactured in a controlled environment. The entire process does not have to be done under aseptic conditions, but the firm must have established the point in the process where aseptic controls begin.

Observe the aseptic processes directly, when possible, and evaluate aseptic technique. Evaluate all connections and transfers to ensure that they are made in an aseptic manner.

Review all cleaning and sanitization procedures for the aseptic core and evaluate whether the cleaning agents are used according to results of validation studies and whether surfaces are monitored to demonstrate continued efficacy. If filling needles are re-used, the cleaning should be validated.

If the duration of filling is lengthy, determine if time limits have been set 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 interruption of the fill, should it occur.

Some bulk products are held after sterile filtration prior to filling. Determine whether the holding period and storage conditions have been validated.

Procedures must be in place for limiting access to controlled and classified areas.

Determine if the sterilizing filters were validated for product compatibility and microbial retention and are adequate for their intended use. Evaluate validation of sterilization of filters. Ensure that filters are evaluated prior to use to ensure they meet specifications. Integrity testing should be performed on filters post-fill and results should be in keeping with manufacturer's and validated specifications.

Review the program 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.

Evaluate the firm's aseptic processing areas (filling and lyophilization) 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*.

Determine whether Class 100 conditions have been validated and are maintained in areas in which sterile product and components, including container/closure systems, are exposed. When alert limits are exceeded, microbial identification should be performed.

Products must be maintained in a controlled environment throughout the process and have specified action and alert limits for which the firm can provide a meaningful rationale. Bioburden alert and action levels should be established for intermediates. Ensure that the manufacturer has established microbial specifications and a monitoring program to include identification of the types of microorganisms present.

Investigators should examine the system to determine if there are any ports of entry for adventitious agents.

b. Endotoxin levels

There is often no step to remove endotoxin from the product, so it must be controlled from the beginning of the process. If there is a step in the manufacturing process to remove endotoxin, it is usually early in the process, so the remainder of the process must be carefully controlled against contamination. Investigators should review the manufacturing facility and process for potential opportunities for contamination. Review the firm's procedures to monitor the bioburden level throughout the manufacturing process to ensure the level is controlled.

Ensure that:

- Production is 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 are in place and followed; and

- Precautions are taken to prevent contamination or cross-contamination in areas in which operations for the preparation of cell banks and product manufacturing processes which are capable of promoting microbiological growth are monitored for bioburden on a routine basis.

c. 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.

Examine the connections between vessels. If the system is closed, review the connections to determine there is no break in the system. Review the batch records and ensure that all steps in the process are recorded.

d. Disruption and harvest

Disruption (when appropriate) and harvesting of the product is done using either chemical, physical, or enzymatic means. Review the batch records to determine if the firm is using the approved method. All essential parameters should be documented.

e. Purification

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

f. Viral inactivation/removal

For products derived from cells 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.

Report on the viral inactivation/removal steps used by the manufacturer. Ensure that the parameters specified in the batch record were achieved such that the validated process for viral inactivation/removal is accomplished. If changes were made to the process, which did not require submission of a supplement to *CDER*, ensure that the changes were validated.

g. Lyophilization

Review and observe, when possible, transfer of product to the lyophilizer. This transfer should be done under Class 100 conditions, or as otherwise approved by *CDER*. Ensure the lyophilization

process is performed in accordance with validated parameters, including the placement of products in the lyophilizer.

If the vials are overlaid with gas (usually nitrogen) evaluate the firm's procedures for integrity testing of sterilizing filters, sterilization, and replacement, and ensure that the procedures used have been validated.

3. Validation

a. 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. Ensure that 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.

b. Computer

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

c. Shipping

Ensure that shipping conditions have been validated, including containers and methods. If the firm has contract manufacturers that perform some or all of the manufacturing steps, ensure that the shipping conditions for the partially processed materials have been validated and the validated processes are followed and documented. The shipper must assure the product is maintained at the proper temperature during shipment and must have records to demonstrate this.

4. Testing and Laboratory controls

A large component of every GMP inspection is the inspection of the laboratory. Laboratory equipment and procedures must be qualified and validated. Required testing is defined in the regulations and in the approved license application.

Review the records of in-process testing and ensure that all test results are recorded. If in-process material failed a test, determine the disposition of the material. If the material was used in a finished product and released, review the records of the justification for releasing the product and ensure the firm had adequate justification. The firm must have records to show whether the product has passed or failed acceptance criteria.

Review and evaluate the firm's methods for sampling and testing products for identity, potency, safety, sterility, and conformance with final specifications. Ensure that the firm is using test methods, which have been appropriately validated for all products on which they are used. Review raw testing data and compare to those reported into the batch production records. Review the SOPs for investigating product test failures and ensure they are adequate and being followed. Determine if reference standards for testing are in date and on a suitable schedule for determining continuous suitability for use. Review laboratory records for the results of tests and their comparison with established standards. Observe the performance of key tests for adherence to approved procedures.

Investigators should review a laboratory's quality management procedures and enough raw data to be assured that data are authentic and reliable. The investigators should assure:

- Data are reliable/ complete, and authentic.
- Data were generated in accordance with GMPs, including documentation and review.
- Laboratory equipment is properly calibrated and qualified.
- Analysts and supervisors are adequately trained.
- Appropriate application of statistical methods, including averaging.

Retesting may be allowed under strictly defined conditions. If a manufacturer performs retesting, ensure there are procedures in place to determine when retesting is appropriate, how retesting should be performed (sampling, duplicates), and how results should be interpreted. The procedure may not permit testing to be performed an infinite number of times. A manufacturer may also retest a sample or collect an additional sample if an investigation shows that the original test or sample collection should be invalidated.

5. Environmental controls/monitoring

There should be a comprehensive environmental monitoring program, which includes monitoring for non-viable and viable air particulates, surface viables and, in the aseptic filling areas, personnel. Procedures should address frequencies and locations for monitoring, alert, and action limits for each area, and corrective actions to be taken when limits are exceeded. Actions taken when limits are exceeded should include adequate investigation into the source of the problem, potential impact on the product, and measures taken to prevent recurrence.

Generally, less frequent monitoring is acceptable in areas in which upstream steps are performed. There, steps may be performed in unclassified, but "controlled" environments (ones with some level of particulate controls). As the process moves further downstream, more frequent monitoring is expected. Monitoring should be performed during production.

Determine whether the firm has procedures in place for adequate environmental monitoring and if the procedures are followed and if the procedures describe what to do with any affected product. Determine

what steps the firm takes if action or alert limits are exceeded and review any investigations performed. If the limits were exceeded during any production runs, determine the disposition of the product.

Review the schedule and procedures for media fills. Review the records for the media fills performed since the previous inspection. If there were any excursions, determine what corrective action the firm took.

Evaluate the firm's media fill procedures and test results. Ensure that all operators and shifts are covered. Determine if media fills encompass all events occurring during normal operations. Determine if all package sizes are represented. This may be done by bracketing of large and small size containers, particularly when vial openings are similar for many sizes represented. Worst case assessments, including any manual manipulations, transport, loading and unloading, or maintenance functions should be included. If product is lyophilized, this process should be mimicked during media fills (media should not be actually run through the lyophilization cycle during a media fill). Determine the alert and action levels, and evaluate whether the action taken when these levels are reached or exceeded is appropriate. If excursions occurred, determine whether investigations were conducted and appropriate corrective action taken. Determine the frequency of media fills after the initial validation.

6. Cross contamination

Cross-contamination may be a significant concern in a facility that manufactures more than one product. The firm's method for separating the products, either by space or time, should be reviewed to ensure there is no potential for cross-contamination. If equipment is not dedicated to one product, records of cleaning and cleaning validation should be reviewed. If personnel work in more than one area, the employees should be trained to ensure that they take adequate precautions to prevent cross-contamination when they pass from one area to another.

7. Non-conforming product

a. Investigation

Determine if the manufacturer has established and implemented procedures for control of nonconforming product that include a determination of the need for an investigation, and a written evaluation of the investigation, if conducted.

Request a list of all failed final and in-process lots, and a list of all deviations. Determine whether any lots that failed to meet any specifications have been released. This includes any lots or portions of lots, including components or raw materials, that have been rejected either in-process or during finished product testing for failing to meet any or all of the product's specifications.

Review records for proper disposition of nonconforming products to assure that use of nonconforming product has not resulted in the distribution of unsuitable products. Document and report on any distribution of out-of-specification products.

For biotech products, the manufacturer should conduct an investigation when the WCB does not generate necessary growth when used according to established procedures or if usage deviates from the established schedule. If these events occurred, report on the investigation conducted and the findings.

b. Reworking/reprocessing

A firm may rework or reprocess a product or in-process material that fails to meet specifications. Inspections should emphasize the investigation into the non-complying result as well as the corrective action resulting from the investigation.

A manufacturer may also blend or pool product to recover clinically useful and economically valuable material. It is unacceptable to blend lots to reduce the level of adulterants, e.g., endotoxin, below action limits, unless a manufacturing step designed to reduce the adulterants is used, and the process is validated.

It is unacceptable for material from final containers in which bacterial growth occurs to be used for further manufacturing.

Determine whether the manufacturer has established and maintains procedures for reworking/reprocessing.

Report on any reprocessing/reworking, i.e., re-pooling, blending, etc. that is performed. Identify the products that undergo such procedures; the conditions under which such procedures are performed; and who approves the reprocessing plan. If failed lots are reworked, determine if the firm conducted and documented an investigation to determine the cause of the failure before reprocessing the product.

c. Complaints

The firm must have written complaint handling procedures, which should include obtaining information such as the identity of the complainant and of the complaint product, the lot number, and factors that contributed to the alleged deficiency.

When reviewing complaints, check for Adverse Event Reporting (AER) reportable events. Determine if the appropriate reports were filed with FDA within the time frames required in the regulations.

Review complaints received since the last inspection. Ensure that all communications involving product deficiencies that meet the definition of a complaint are treated as such and are reviewed, evaluated, and investigated unless a similar complaint has been investigated and another investigation is not necessary.

Ascertain the firm's basis for determining the significance of complaints and how the follow-up is conducted. Determine if oral and telephone complaints are documented.

Review and analyze complaints to identify existing and/or potential causes of nonconforming product or other quality problems. Determine if the firm has performed a sufficient complaint investigation.

If defective product is returned to the firm, determine the disposition of the product and if the firm has a procedure for this process.

d. Recalls

Determine if the firm conducted any recalls since the last inspection. If the firm did conduct any recalls, determine the disposition of the affected products. If the firm did not report the recall to FDA, collect attachment information as described in the Regulatory Procedures Manual. If the recall was due to ***a manufacturing deviation, determine if the firm filed a product deviation report.***

e. Product deviations

21 CFR 600.14(a) requires manufacturers of licensed biological products to promptly notify FDA, of deviations in the manufacture of products that may affect their safety, purity, or potency.

If another location handles product deviation reporting, include in the EIR the name and address of the location and the name of the person responsible for handling them. Collect copies of any SOPs that describe how the location being inspected interacts with the office responsible for handling these reports.

Ensure all product deviations that occurred were reported to FDA. If confirmation of their submission to FDA is needed, contact ***DMPQ, Investigations & Pre-approval Compliance Branch, HFD-322.***

f. Adverse Experience Reports (AERs)

21 CFR 600.80 requires that serious, unexpected adverse experiences associated with the use of a biological product in humans be reported to FDA within 15 days of initial receipt of information or periodically, depending on the seriousness of the adverse reaction.

Review records of adverse events received by the manufacturer and ensure that reports have been submitted to FDA as required. If there are questions or concerns regarding the seriousness of, and therefore the reporting requirements for, an adverse experience, contact ***DMPQ, Investigations & Pre-approval Compliance Branch, HFD-322.***

8. Changes to be reported

Licensed manufacturers are required to conform to the standards established in their license applications as well as applicable sections of the regulations. 21 CFR 601.12 requires that manufacturers inform FDA

about important changes in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling, from that in the approved license application. (See references 4, 11, and 12).

The type of notification is based on the potential risk of the change having an adverse effect on the safety or effectiveness of the product. In general, changes which have a minimal effect on the safety or effectiveness of a product may be implemented before being reported to FDA; however, manufacturers are required to include such changes in annual reports to the agency. Data relevant to changes reported in annual reports (i.e., validation data) must be made available during FDA inspections.

When a change has a moderate potential to have an adverse effect on 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, the manufacturer may distribute product manufactured using the change.

When a change has a substantial potential to adversely affect the safety or effectiveness of a product, product manufactured using that change cannot be distributed until FDA approves a license supplement describing the change.

Request a list of changes or modifications made to products, processes, quality control, equipment, facilities, systems, and/or responsible personnel that have not been submitted to FDA as either a supplement or in an annual report since the last inspection, and include it as an exhibit in the report.

Review any changes, which the manufacturer has determined do not require a supplement and that have not yet been included in an annual report to FDA, and describe them in the inspection report. 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 *DMPQ, Investigations & Pre-approval Compliance Branch, HFD-322.*

9. GMP

a. Equipment

Ensure that key equipment and procedures (those that could affect product quality, e.g., autoclaves, heat treatment baths, filling equipment and product contact surfaces, filling and closing of containers, lyophilizers, depyrogenation equipment) used by the firm are suitable for their intended uses. Determine if periodic *requalification* of the equipment is performed. Evaluate the adequacy of the equipment *qualification*.

Ensure that the firm has SOPs for operating the equipment and that the instructions are readily available to the personnel performing the operations.

Key equipment should be appropriately cleaned and tagged as to status, identified, calibrated, inspected or checked, *qualified, and requalified* when necessary, according to a written program.

Determine if the firm has maintenance schedules in place and, if so, that the schedules are followed.

For columns used in purification steps, ensure the firm has procedures in place for cleaning and storage of the column housings and column media and that the procedures are followed. There should be an established life span for each column type (i.e., number of runs or months of use). Ensure that columns are not used beyond their established life span.

i. Cleaning

Review SOPs for equipment cleaning procedures and determine if they are validated and followed. The validation should have included an evaluation of the cleaning efficacy of dedicated equipment and assurance that detergents, if any, are removed during cleaning. The firm should have established residual limits and be using an assay appropriate to detect any contaminants. For multi-use equipment, the cleaning validation should have established that there is no carry-over between products such that the safety and efficacy of subsequent products is compromised. There should be periodic monitoring of the validated cleaning procedure to ensure continued cleaning effectiveness.

ii. Calibration

Calibration should be performed according to a prescribed schedule conforming to the equipment manufacturer's recommendations.

All testing, measuring, and monitoring equipment should be calibrated, periodically checked for accuracy, and recalibrated according to an established schedule. Determine the frequency, and the source of the standards used.

Verify that calibration procedures include specific directions and limits for accuracy and precision, and provisions for remedial action.

Examine records of major manufacturing equipment calibration, checks, inspection, maintenance, cleaning, sanitizing, and use; and laboratory equipment calibration.

b. Buildings

Manufacturers must establish and maintain procedures to adequately control environmental conditions where they could reasonably be expected to have an adverse effect on product quality. Lighting, ventilation, temperature, humidity, air pressure, filtration, airborne contamination, and

static electricity are among many conditions to be considered for control. Environmental monitoring must also be performed where appropriate to the operation; see Section B.5.

Observe the state of repair of the facility and determine whether the firm has a program for updating facilities and ensuring that changes to systems are validated/revalidated, as appropriate, and that modifications to the facilities are approved by *CDER*, when appropriate, and do not adversely affect production areas and product safety.

Determine whether cleaning and disinfecting practices, particularly for manufacturing areas, sterile filling suites, and the aseptic core area are adequate and validated.

Examine the procedures and areas for segregating and storing raw materials; quarantined rejected, in-process, and released products.

Make certain that buildings:

- Are appropriately constructed to prevent, reduce, and control potential contaminants and support the environmental control program;
- Have sufficient space for manufacturing, receiving, packaging/labeling, storage, etc.; and
- Are designed to allow proper cleaning, maintenance, and other necessary operations.

Review procedures for controlling and monitoring pressure differentials, humidity, and temperature. Procedures should include actions to be taken when results are not within established limits. Ensure that the impact of out-of-limit results on the product is adequately addressed.

i. Spore-forming products

If the firm uses spore-forming products, these materials must be physically segregated from areas in which non-spore-forming materials are processed.

This requires, at a minimum, the building in which the spore-forming organisms are processed be either a separate building or be physically separated from other processing areas; that there is a separate entrance; and that the equipment used in the processing areas for the spore-forming organisms be used exclusively in that area.

ii. Water systems

Review water system diagrams and inspect the system to determine that the diagrams adequately reflect the current as-built conditions. While inspecting the system, look for dead legs and evidence of leaks. All valves and connections should be of sanitary design. Source water used to feed the water treatment system should meet EPA or comparable potable drinking water standards as directed in the USP. If the source water is from a

municipal source, records of EPA tests provided by the municipality may be accepted; however, periodic testing of identified parameters should be conducted to ensure that the water meets standards as it enters the firm.

Determine the source of water and how and with what frequency incoming water is sampled and tested. All water treatment components, e.g., sand filters, carbon filters, deionizing units, and reverse osmosis units, should be maintained according to manufacturer's specifications, and periodically monitored to ensure proper performance. Ensure that SOPs for maintenance, replacement, regeneration, and/or sanitation of water treatment components are in place and followed and that all instruments, gauges, meters, etc., are routinely calibrated.

Water that is within the USP's current water for injection (WFI) specifications is generally used in production of therapeutic drug products. Purified water may be used in upstream processing and for initial rinses of downstream equipment. Potable water may be used as an initial rinse for upstream equipment.

If the WFI system is not a continuous flow design, review the firm's procedures for batching and discarding the water.

Review the firm's procedures and controls for the production, monitoring, and testing of all types of water used and determine if the water quality meets appropriate specifications. Determine how alert levels were established, i.e., were they based on historical data? Determine if the data-generated is monitored, and ensure that procedures include appropriate actions to take when alert and action levels are exceeded.

Ensure that all water storage tanks are equipped to prevent microbial contamination. Evaluate replacement procedures and determine if integrity testing of filters is performed after use.

iii. Clean in Place (CIP) and Sterilization in Place (SIP) systems

For CIP systems, there should be proper control of cycles and periodic evaluation of cleaning efficacy. SIP may also be used in downstream processing areas for sterilization of equipment. As with CIP, there should be proper control of cycles and periodic evaluation of the adequacy of the sterilization.

Determine which equipment, containers/closures, etc., are cleaned and which are sterilized by which process. Evaluate the firm's validation procedures for all CIP/SIP processes.

iv. HVAC systems

The HVAC system should be designed to provide containment or product protection when and where necessary. Negative pressures may be maintained during upstream processing to provide containment. Positive pressures should be maintained in downstream processing areas and the aseptic core. Separate air handling units, or single pass air, should be used in post-viral inactivation areas and the aseptic core.

All HEPA filters should be validated and should be recertified at least annually. Recertification should include integrity testing of the HEPA filters with an appropriate challenge aerosol, e.g., dioctyl phthalate (DOP) or an alternative aerosol that has been determined to have similar or acceptable physical characteristics for detection of leaks; air velocity studies; particle counts, and in aseptic areas, laminarity.

c. Quality Control

Manufacturers are required to establish a quality control unit that has the responsibility to approve or reject all components/ packaging, drug products, labeling, etc. Ensure that the facility has a quality control unit, document the responsibilities of the QC unit, and evaluate whether the QC unit is effective in carrying out its responsibilities. Review and evaluate the firm's quality assurance and quality control procedures and programs.

Review pertinent SOPs, e.g., final product/check-off sheet found in batch records, change/repair controls, alert/action limits and corrective actions taken.

Determine whether specification and procedure changes, changes in work instructions, and other instructional procedures are made through formal processes and controls.

d. Personnel/Training

Determine whether personnel are sufficient in number with the necessary background, training and experience to correctly perform all required functions; and whether training procedures are established to ensure all personnel are adequately trained to perform their assigned responsibilities and to be aware of the potential effects of their improper job performance. Look for any examples of personnel failing to perform or inadequately performing a task. If the facility is a multi-use one, employees that are not dedicated to one operation or area must be trained in all the areas in which they operate.

Ensure that employees are trained prior to performing a task and review documentation of training. If training is performed in-house, review the qualifications of the instructors and the process for evaluating the success of the training.

e. Waste processing

Review the firm's procedures for disposal of manufacturing waste. The procedures should include provisions for inactivation of infectious agents and holding conditions. The procedures should protect against cross-contamination. The firm should also have procedures for handling accidental spills.

f. Labeling/packaging

Labeling requirements applicable to biotechnology-derived drug products 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 *CDER*.

Ensure that products are labeled as approved by *CDER*.

Labeling deficiencies should not be included on Form FDA 483s unless inclusion of the observation has been approved by *CDER*. Contact *DMPQ, Investigations & Pre-approval Compliance Branch, HFD-322* if there appear to be labeling deficiencies in the firm's products.

10. Records

Records required by the cGMP regulations must be maintained at the manufacturing facility or at another location reasonably accessible to responsible officials of the manufacturer and to FDA investigators. For facilities that maintain records electronically, see also section B.3.b. (Computer).

a. Master production

The master production record contains the documentation necessary to produce the drug product. The master production record should have complete manufacturing and control instructions, sampling and testing procedures, and specifications for the product. It should also include information about the container, closure, and packaging materials, including labeling.

Ensure that the master production record contains or references the procedures and specifications that are current on the manufacturing floor.

b. Batch Records

Verify that batch records representing individual lots exist for all finished products manufactured, and that the records show the processes, tests, reworking/reprocessing the drug went through from the beginning of manufacturing to distribution and reflects that all operations, processes, etc., described in the master production record were accomplished.

Review batch production and control records of representative lots manufactured since the last inspection for completeness and for review and approval by the quality control unit before release

of each lot. Ensure that the batch records reflect the actual process being performed, and that the process being performed is the same as that which was validated.

c. Distribution

Review distribution records cross-referenced to final inspection and release and quarantine record to verify that no obsolete, rejected, or deteriorated product was used or distributed.

Ensure that distribution records contain or make reference to the location of the name and address of the initial consignee, identification and quantity shipped, date shipped, and control/lot numbers used.

d. Stability

Stability records are required to support labeled dating periods. Ensure that stability records show that the final products and their individual components were tested using standardized panels and that real time stability is evaluated at appropriate storage and shipping temperatures, using specimens with varied reactivities in the readable range. Verify that the firm retains samples and performs testing, where appropriate, for the entire dating period.

11. Lot release

21 CFR 610.2(a) states that a manufacturer may be required to send samples of any lot of any licensed biological product together with protocols showing results of applicable tests on the lot to *CDER*; and that upon notification by the Director, *CDER*, a manufacturer shall not distribute a lot of a product until it is released by the Director.

In a notice published in the Federal Register in December 1995, the Agency eliminated the requirement for routine lot release for specified biotech products. Manufacturers must still ensure that the products meet the manufacturer's lot release specifications prior to distribution. *CDER* may require that these products be submitted for *CDER* lot release if a manufacturer demonstrates an inability to consistently manufacture product in accordance with specifications.

Some manufacturers of biological products have, through approved license supplements, received exemptions from lot release and are on a "surveillance" program. Manufacturers on surveillance are required to submit samples and/or protocols to *CDER* at specified intervals, but they may market their products without receiving lot release. If a regulatory action is taken against a manufacturer whose products are not currently subject to *CDER* lot release, its product (s) may be removed from surveillance status.

Review representative lot release test records, especially for those products on surveillance or exempt from lot release, to ensure that all specifications have been met. Check whether any lot has failed to be released and if so, the reason for failure and the disposition of failed lots. For products that are subject to FDA lot release, review records to ensure that products were not distributed prior to release of the lots by FDA.

C. *Sample Collection

CDER may request sample collection and will provide specific instructions. If official samples are not requested, but the inspection team believes their collection is warranted, contact the Branch Chief, Case Management and Guidance Branch (HFD-326), 301-827-8941, for guidance prior to collecting samples.

Collect any samples of a potentially biohazardous nature in accordance with IOM section 145.

If significant deviations are noted, collect a documentary sample in accordance with section 405.2 of the IOM.*

D. Reporting

1. Record any deviations from GMP, AER, or other applicable regulations on the FDA Form 483, Inspectional Observations.
2. Notify ORO and *CDER/OC* immediately if a potentially serious health hazard exists.
3. Briefly report on all major areas or systems investigated as outlined in this part, 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.
4. The ORA Core Team investigator, as lead, will coordinate the preparation of the report. The report will be endorsed, classified, and submitted in accordance with agency policy and procedures. Reports should be submitted within established agency time frames.
5. Domestic inspections: Send a copy of each establishment inspection report, including endorsement and classification, to *CDER* (see Part VI, Program Contacts). The exhibits should not be included unless specifically requested. The original EIR, including endorsement and exhibits, should be forwarded to the firm's home district. A copy of the coversheet and endorsement should also be sent to ORO, HFC- 100. The home district will be responsible for releasing the EIR under FMD 145 and for filling any FOIA requests.

Foreign inspections: The original EIR, endorsement, and exhibits should be sent to *CDER/OC/FIT, HFD-325*. A copy of the endorsement and coversheet should also be sent to ORO, HFC- 100. *CDER* will be responsible for releasing the EIR under FMD 145 and for filling any FOIA requests for the EIR.

PART IV - Analytical

No field analyses are projected under this program.

Routine sample collection under this program is not anticipated. Consult with *CDER* program contact identified in Part VI before collecting samples for agency analysis, except for documentary samples for interstate commerce.

PART V – REGULATORY/ADMINISTRATIVE STRATEGY

It is essential to promptly evaluate any violative conditions observed during an inspection in order to ensure product safety and effectiveness. This evaluation and any resultant recommendation for action will be conducted using the procedures set forth in the Case Processing SOP established for Team Biologics/Core Team.

Regulatory /Administrative Follow-Up

Significant Deviations

Significant, documented deviations from the law, regulations, or license may warrant regulatory and/or administrative action. Such deviations may include the following violative conditions found during inspections of licensed biotechnology-derived therapeutic products (this list is not intended to be all inclusive):

1. Organization and Personnel [211.22 - 211.34 and 600.10]
 - Personnel engaged in the manufacture of a drug product are not adequately trained in the particular operations they perform and in cGMP regulations.
 - Adequate protective apparel for personnel engaged in the manufacture of a drug product to protect the product from contamination was not provided.
 - There is no procedure to ensure that SOPs, including any changes, are reviewed and approved by the quality control unit.
2. Buildings and Facilities [211.42 - 211.58 and 600.11]
 - Separate or defined areas or such control systems as necessary to prevent contamination or mix-ups are not maintained.
 - Non-viable particulate monitoring is not performed in critical or controlled production areas.
 - Surface monitoring for microbial in critical areas is not performed.
 - Microbial and particulate counts are not performed during periods of activity.
 - The effectiveness of the cleaning and sanitizing procedures have not been established.
 - Written procedure describing the schedules, methods, equipment, and materials to be used in cleaning buildings and facilities have not been established or followed.
 - Buildings are not maintained in a clean and sanitary condition.

3. Equipment [211.63 - 211.72 and 600.11]
 - Failure to establish, validate, and follow procedures for cleaning and maintenance of equipment.
 - Equipment is not routinely calibrated.
4. Control of Components and Drug Product Containers and Closures [211.80 - 211.94]
 - Rejected components were stored in a general storage area and there was no labeling or other method used to identify these components as rejected.
 - Identity tests and periodic potency retests of components are not performed.
 - Expired components are not removed from inventory.
 - Inventory records of components do not include sufficient information to allow tracking of a component to a drug product batch or lot.
5. Production and Process Controls [211.100 - 211.115]
 - Failure to establish and/or follow adequate written procedures for production and process control.
 - Investigations of process failures were not performed and/or corrective actions were not taken.
 - There are no written procedures or specifications for selection of stock cultures used in production.
 - There are no written procedures defining conditions for shipment.
 - There were no records of investigations to determine sources of contamination associated with environmental monitoring excursions.
 - There are no formal written procedures for installation and performance qualification of production equipment
 - There are no written procedures for reprocessing or reworking batches that do not conform to standards or specifications.
 - The production processes are not validated.
6. Holding and Distribution [211.142 - 211.150]
 - Distribution of each lot cannot be readily determined.
7. Laboratory Controls [211.160 - 211.176]

- There is no data to support the established limits and/or specifications.
 - There is no testing performed prior to distribution to ensure that product meets its final release specifications.
 - Failure to establish a formal written stability protocol, defining conditions and parameters for evaluating the stability of a drug product.
 - Reserve samples are not retained.
8. Records and Reports [211.180 - 211.198]
- Failure to maintain records that include an individual inventory record of each component, and for each component, a reconciliation of use.
 - The master production record does not provide adequate specifications for various steps in the manufacturing process.
 - Acceptance specifications for in-process tests are not defined.
 - The master formula does not define specifications for potency or describe other parameters used as criteria for release.
 - There is no record of review of batch production records by facility personnel.
 - Batch production records do not document actual yields produced.
 - Failure to maintain distribution records.
9. Changes to an Approved Application [601.12]
- Failure to notify the FDA of changes in location, equipment, responsible personnel, and manufacturing methods, as otherwise required
10. General Biological Products Standards; Identity [610.14]
- The identity test is not specific for each drug product as it will not adequately identify it as the product designated on final container and package labels and circulars, and will not distinguish it from any other product being processed in the same facility.
11. General Biological Products Standards; Purity [610.13]
- Failure to establish an adequate test for product purity and validate that the chemicals used in the production of the product and any adventitious agents are removed from the final product.

Regulatory Actions

A firm's written corrective action plan in response to an FDA Form 483 does not preclude consideration of regulatory or administrative action. If voluntary action is not appropriate or accomplished, or the deviations pose a threat to the consumer, regulatory and/or administrative action should be recommended. As stated above, the evaluation of inspection findings and any resultant recommendation for enforcement action should be conducted in accordance with the procedures set forth in the Team Biologics Case Processing SOP.

The decision on the type of action to recommend should be based on the seriousness of the problem, the most effective way to protect the consumer, and the regulatory history of the establishment. It is essential that the importance and relative availability of the product (s) as well as the potential adverse effect of GMP deviations on the finished product (s) be considered in determining appropriate regulatory and/or administrative action. Available options for regulatory actions include Warning Letter, license revocation and suspension, seizure, injunction, prosecution, recall order. The Regulatory Procedures Manual should be used, as a reference to assist in determining which regulatory action is appropriate. For additional assistance, the *CDER/DMPQ* may be contacted.

Warning letters: *CDER concurrence must be obtained for all Warning Letters issued under this program.*

PART VI – REFERENCES AND PROGRAM CONTACTS

REFERENCES

1. Federal Food, Drug and Cosmetic Act, as Amended.
2. Public Health Service Act, Biological Products.
3. Title 21, Code of Federal Regulations, Parts 211, 314, 600, 601, 610.
4. Investigations Operations Manual (IOM).
5. Regulatory Procedures Manual (RPM), Chapter 4, Advisory Actions; Chapter 5, Administrative Actions; Chapter 6, Judicial Actions; and Chapter 10, Other Procedures.
6. Compliance Policy Guides, Subchapter 130; Subchapter 200; and Subchapter 400, section 480.100.
7. Compliance Program Guidance Manual, CP 7356.002, Drug Process Inspections; CP 7356.002A, Sterile Drug Process Inspections; and CP 7356.002F, Bulk Pharmaceutical Chemicals.
8. Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products, CBER, July 1997.
9. Guideline on General Principles of Process Validation, May 1987.
10. Guideline on Sterile Drug Products Produced by Aseptic Processing, Center for Drugs and Biologics and ORA, June 1987.
- *11 Draft Guidance for Industry – Sterile Drug Product Produced by Aseptic Processing – Current Good Manufacturing Practice, CDER, CBER, and ORA, August 2003 *
12. Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics, CDER, CBER.
13. Guide to Inspections of Dosage Form Drug Manufacturers - CGMPs, ORA/ORO/DFI, October 1993.
14. Guide to Inspections of High Purity Water Systems, ORA/ORO, June 1993.
15. Guide to Inspection of Bulk Pharmaceutical Chemical Manufacturers, September 1991.
16. Guide to Inspection of Pharmaceutical Quality Control Laboratories, July 1993.
17. Guide to Inspection of Microbiological Pharmaceutical Quality Control Laboratories, July 1993.
18. Guide to Inspection of Validation of Cleaning Processes, July 1993.

19. Biotechnology Inspection Guide.
20. Guide to Inspections of Lyophilization of Parenterals, ORA/ORA/DFI, July 1993.
21. Points to Consider in the Manufacture of Recombinant DNA Derived. Products, Monoclonal Based In Vitro and In Vivo Products, CBER.
22. FDA Policy for the Regulation of Computer Products, CDRH.
23. Biosafetv in Microbiolocrical and Biomedical Laboratories. DHHS.
24. United States Pharmacopeia, Current Revision and Supplements.
25. Team Biologics/Core Team Case Processing SOP, Operations Group.

PROGRAM CONTACTS

***CDER**

Send copies of reports and questions regarding the instructions in this program (except as otherwise directed):

Branch Chief
Division of Manufacturing and Product Quality
Investigations & Preapproval Compliance Branch (HFD-322)
11919 Rockville Pike
Rockville, MD 20852

301-827-8942; fax 301-827-8909

Otherwise, please refer to the main program, 7356.002, for contact information.*

PART VII – CENTER RESPONSIBILITIES

Inspection Profiles and Information

*The Investigations & Preapproval Compliance Branch (HFD-322) *is responsible for providing appropriate background material, including license and lot release information and copies of applicable correspondence and reports, to investigators prior to scheduled inspections. This office will also serve as the point of contact for any technical questions raised during inspections, and will be responsible for ensuring the investigators receive responses in a timely manner.

Program Review and Evaluation

CDER will monitor this program and evaluate reports of inspections. Results of evaluations will be shared with the field, ORA/ORO, and interested *CDER* units. *CDER* will also coordinate and/or prepare an annual review and evaluation of this compliance program.