

CHAPTER 45 - VACCINES AND ALLERGENIC PRODUCTS

SUBJECT: Inspections of Licensed Allergenic Products		IMPLEMENTATION DATE October 1, 1998
		COMPLETION DATE September 30, 1999
DATA REPORTING		
PRODUCT CODES	PROGRAMS/ASSIGNMENT CODES	
57GY-□□	45001 - GMP inspections 45001A - pre-license inspections	

FIELD REPORTING REQUIREMENTS:

Domestic Inspections: A copy of each establishment inspection report (EIR), including endorsement and classification, should be submitted to CBER, Office of Compliance and Biologics Quality, Team Biologics Liaison Staff, HFM-604. Exhibits should not be included unless specifically requested.

Foreign Inspections: The complete original EIR, including exhibits, should be forwarded to CBER, Office of Compliance and Biologics Quality, Team Biologics Liaison Staff, HFM-604, regardless of classification.

PART I - BACKGROUND

Within the FDA, the Center for Biologics Evaluation and Research (CBER) has been designated as the lead Center for regulating allergenic products, including source materials used in the manufacture of allergenic products. These products are used for the diagnosis and treatment of individuals with sensitivity to certain materials. Thorough scrutiny must be given to their manufacturing and compliance with applicable regulations and standards.

The intent of this program is to provide uniform guidance to FDA Office of Regulatory Affairs (ORA) and CBER personnel to evaluate the conditions under which licensed allergenic products and unlicensed source materials are manufactured, and to enforce the applicable requirements.

CBER Product Responsibilities

Under the Public Health Service Act (PHS Act), CBER licenses allergenic products which are used for the diagnosis and treatment of individuals with sensitivity to various materials. Allergenic products are biological products which 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).

Allergenic source material suppliers are not required to register or list, and they are not licensed. These materials are not finished drug products, so manufacturers cannot be held to the requirements in Part 211. Source materials are components of a drug, however, so they must be manufactured in accordance with the general principles of GMPs.

Background

Allergenic products can take two forms - injectable products or 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; allergen test patches are not.

This program is not intended to address allergen test patches, but some of the principles may be applicable to those manufacturers.

Manufacturing

Production of allergenic drug products should take place in a controlled environment. After extraction of the source material with a buffer solution, the material is subject to a clarification process, which removes large particles. The products are passed through a series of filters, the final one being a sterile filter. Injectable products are then filled aseptically, and may be distributed in a number of forms, including lyophilized or final diluted form.

Standardized vs. Non-standardized

The FDA has determined that a number of allergenic products must be in a standardized form. Currently, there are 19 standardized allergens. Standardized allergens must be tested for safety, sterility, potency and identity, and must also be subject to stability testing. Standardized allergens are also subject to CBER lot release. Non-standardized allergens are not subject to CBER lot release testing, and must only be tested for safety and sterility.

Team Biologics

Until the mid 1990s, most licensed allergenic manufacturers were inspected solely by CBER. Since then, many inspections have been conducted jointly by CBER and Field investigators, with CBER leading the inspections. Responsibility for performing the biennial inspections will be transferred to the Team Biologics/Core Team in October 1998, and the inspections will be organized in accordance with the procedures developed by the Core Team under the Team Biologics program. The Compliance Action Team (CAT), comprised of CBER and ORA compliance personnel, will 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 SOP. 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.

PART II - IMPLEMENTATIONOBJECTIVES

- To ensure the safety and effectiveness of allergenic products by determining their compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act); the Public Health Service Act (PHS Act); the applicable regulations, including drug GMP regulations (21 CFR Parts 210 and 211) and Biologics regulations (21 CFR Parts 600-680); and with standards and commitments made in license applications and/or supplements.
- To provide information and guidance to investigators assigned to perform biennial or for cause inspections of manufacturers of allergenic products.
- 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.

PROGRAM MANAGEMENT INSTRUCTIONS

Firms covered under this program include all licensed manufacturers of allergenic products and unlicensed source material suppliers. Allergenic patch test manufacturers are not included in this program.

Workplanning for these inspections will be coordinated by Team Biologics. Each allergenic product manufacturer and its CBER-regulated 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 CBER product specialist participating. The inspection team may include other ORA or CBER members, as necessary, to assure appropriate coverage of the facility. If CBER participation is not possible, the Core Team alone will conduct the inspection.

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. INSPECTION PROCEDURES

Review and use applicable sections of Chapter 5 of the Investigations Operations Manual; Compliance Program 7356.002, Drug Process Inspections and 7356.002A, Sterile Drug Process Inspections; guidance applicable to the manufacture of allergenic products; and licensing, inspectional information, and other pertinent documents provided by CBER. 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 allergenic products.

Allergenic product manufacturers are subject to the regulations in 21 CFR Parts 600-680, in addition to the regulations and standards in Parts 210 and 211. Licensed allergenic product manufacturers 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 CBER/Team Biologics Liaison Staff (TBLS) for assistance. If there is a contradiction between the approved license and anything in this program, the manufacturer should comply with the license commitments.

Allergenic source material suppliers are subject to the requirements in 21 CFR Parts 600-680. Because they are not finished product manufacturers, they are not subject to the drug GMP regulations in Part 211. They are required to comply with GMP in a general sense, to assure the products have the quality, purity, identity they purport to possess. If there are questions regarding the appropriateness of a particular finding as it pertains to an allergenic source material supplier, the Team Biologics CO should review the finding before it is included on an FDA-483.

The approach to individual inspections will be developed by the Team Biologics Core Team, in conjunction with CBER/TBLS and the home district. Products needing special coverage will be addressed as part of the inspection approach.

B. INSPECTION1. Source Material Suppliers

The source material contains the active substance, which is responsible for the allergic response. Source materials and source material manufacturers are not licensed; source material manufacturers are not required to register. Specific criteria for

source materials can be found in 21 CFR 680.1(b) and (c).

Each step in the process to manufacture a source material should be documented. There should be procedures and equipment in place to prevent cross-contamination or introduction of contaminants. If materials are held at any point prior to further processing, the establishment should have procedures describing storage conditions and time limits.

The following areas are not applicable to all source material suppliers, but should be reviewed where appropriate.

a. Inoculation and propagation

Ensure the source of the material is identified. Review test records to determine that the material meets specifications, including purity, identity, quality, and strength.

b. Harvest

Each step in the harvesting process should be documented, including separation of the source material from the propagation system by precipitation, centrifugation, and/or filtration. Review the criteria for harvest, determination of yields, and criteria for pooling harvests, if applicable.

c. Downstream processing

Review the records for inactivation of the mold and viability testing. For any product that did not meet release or acceptance criteria, determine the disposition of the material.

d. Purification

Document the methods used for purification. Determine if the firm pools materials, and ensure that pooling is not performed to bring substandard materials into specification. Review any testing records and determine the disposition of any material that did not meet specifications. Ensure that the levels of residual chemicals, reagents, solvents, etc. were within the allowable limits.

e. Specific source materials

i. Animal source materials

Animal source material must meet the applicable requirements of 21 CFR 600.11(f) and 680.1(b)(3). Investigators should ensure that live animals are in good health as attested to by someone qualified to make the determination (i.e., a veterinarian). Ensure that animals of the equine genus are treated to maintain immunity to tetanus and that reports of any

diseases in 680.1(b)(3)(iv) were reported to CBER as required.

- ii. Source materials derived from molds [680.1(b)(iii); 610.18; 600.11(e)(3)]

The manufacturer should have an established stock culture system in place to ensure the stock culture maintains its integrity. Review the details of the system and ensure the procedures are being followed for storage and frequency and limits of stock culture transfers and/or subcultures.

Manufacturers must have a system in place to ensure that cross-contamination does not occur. If the facility works with more than one type of source material, there must be adequate segregation to ensure that the mold materials are kept separate from other types of materials.

2. Finished product manufacturers

a. Components

Manufacturers must keep records with the results of all testing performed on incoming materials. Review the test results to ensure that all testing is performed and results are satisfactory before a material is used in production.

i. Source materials

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 feasible (e.g., if in the same facility or facility in close proximity to the finished manufacturing site), with the instructions provided above for source material suppliers.

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

- the firm has written, approved, specified requirements for the component(s);
- the firm has established acceptance criteria and has test results to show the source material meets the acceptance criteria;
- the firm has documentation from the source material suppliers, showing the material meets specifications;
- the firm has on file a manufacturing summary for the source materials from the source material supplier.

Allergenic product manufacturers must list with CBER the name and address of each source material supplier. The list must be updated annually. Confirm that the source material suppliers are the same as those reported to CBER.

ii. Water

Water used in the processing of allergenic products, including final rinse of containers and closures, should meet the USP specifications for water for injection (WFI). Water used in other activities may be of a lesser grade, but will frequently also be WFI.

iii. Containers/closures

Ensure that the firm has adequate procedures for the receipt, handling, sampling and storage of containers and closures, especially those that are sterile. Review the procedures for acceptance or rejection of containers from the vendor and determine the means by which the firm qualified the vendor.

Review the procedures used by the firm to verify and ensure suitability of the containers and closures, including any testing performed by the firm on the incoming containers. Although endotoxin testing is not required on the allergenic product, firms are required to test the containers and closures for endotoxin. Confirm that endotoxin testing of the containers and closures was performed and was within specifications.

Ensure that sterilization and depyrogenation procedures for product containers and closures are appropriate, validated, and documented, if necessary. Equipment used for these processes should be properly maintained and requalified periodically.

iv. Other components

For components other than those listed above, manufacturers should have established acceptance criteria appropriate to the component and the process. Acceptance criteria should include an evaluation of the bioburden level of the components, where appropriate.

b. Validation

i. Process validation

Investigators should ensure that any changes made to the manufacturing process since the previous inspection have been validated, where appropriate.

ii. Cleaning validation

Ensure that the cleaning process was validated for each product class, and that any changes made to the cleaning process since the last inspection were validated. Ensure that the cleaning process being used is the same as that which was validated.

iii. Computer validation, if appropriate

If the firm is using a computer driven manufacturing process, ensure that the computer system was validated for that use.

If the firm has any computer controlled manufacturing systems, determine if the firm has evaluated the system(s) to see if it will perform properly on and after January 1, 2000. If the firm has performed such an evaluation, report on the systems evaluated, the impact the year 2000 (Y2K) will have on the systems, and, if the systems are not currently Y2K compliant, whether there will be a fix in place by 1/1/2000. Failure to have computer systems in place that are Y2K compliant should not be noted on the FDA-483, unless the problem adversely affects current operations and/or product.

c. Processing

i. Controlled processing

Licensed injectable allergenic products are required to pass the sterility test or have an equivalent method for demonstrating microbiological control. If the manufacturer is not performing testing as required in the regulations, the manufacturer should have an approval from CBER to perform an alternative procedure.

The manufacture of allergenic products should be performed in a controlled environment with specified action and alert limits. Filling of finished dosage form allergenic products must be performed in a controlled area, usually Class 100. Other operations should be performed under controlled conditions, usually Class 10,000 or 100,000.

Cross-contamination may be a significant concern in a facility that manufactures more than one product. Separation of the products, either by time or place, should be reviewed to ensure that cross-contamination is prevented.

Ensure that:

- Production is performed in a controlled environment that prevents an increase in the product's microbial load beyond its specifications
- Procedures to prevent equipment or product contamination by a substance that could reasonably be expected to have an adverse effect on product quality are in place and followed
- Precautions are taken to prevent contamination or cross-contamination in areas in which product manufacturing processes which are capable of promoting microbiological growth are monitored for bioburden on a routine basis
- The air handling system is sufficient to protect the product and the environment, e.g., use of HEPA filtered air.

Manufacturers that use molds in manufacturing allergenic products must exercise special controls to ensure that contamination does not occur.

ii. Manufacturing steps

Ensure that the manufacturing process is the same as that in the approved application or supplement. If materials are stored between processing steps, the storage conditions (time, temperature, etc.) should be validated and followed. If possible, observe all the steps in the manufacturing process.

(a) Aseptic filling

Evaluate validation of sterilization of the filters. Ensure that integrity testing is performed on filters post-fill and that the filters are operating in accordance with manufacturer's and validated specifications. If products are held after sterile filtration, ensure the holding time and storage conditions have been validated.

Review the program in place for qualification of filling operators. This should include monitoring of gowning techniques to ensure compliance. Ensure that written procedures for gowning are in place and followed. A touch plate evaluation should be performed on a periodic, defined, basis.

Media fills: Evaluate the firm's media fill procedures and review test results. Ensure that all operators and shifts are covered and that the media fill represents all volumes filled. If the product is lyophilized, the media fill should mimic the lyophilization process, but the lyophilization process should not be performed on media filled vials.

(b) Lyophilization

If the final allergenic product is lyophilized, observe, if possible, the transfer of the product to the lyophilizer. This transfer should be done under Class 100 conditions, or as otherwise approved by CBER.

Evaluate whether the firm is routinely following validated cleaning and sterilization procedures between product batches.

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

(c) Labeling/Packaging

Labeling requirements for licensed allergenic products are found in 21 CFR Part 610. Specific wording for labeling is reviewed and approved by CBER.

Ensure that products are labeled as approved by CBER. Deficiencies in the product label should not be included on Form FDA 483s unless inclusion of the observation has been approved by CBER. Contact CBER/TBLS if there appear to be labeling deficiencies in the firm's products.

Because no identity testing is performed on non-standardized allergenic products, it is especially important that the products be labeled correctly. If there are deficiencies noted in the manner of labeling, as opposed to the label itself, these deficiencies should be noted on the FDA-483.

The firm should maintain records of labeling usage and reconciliation.

(d) Prescription sets

Prescription sets are manufactured from bulk or stock concentrates in accordance with an individual physician's prescription. The composition of the sets is generally considered to be the practice of pharmacy; 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 cGMP.

d. Environmental monitoring/control systems

Procedures must be in place for limiting access to controlled and classified areas. The flow of personnel should be controlled, especially in mold propagation areas and animal rooms.

There should be a comprehensive environmental monitoring program which includes monitoring for non-viable and viable air particulates, surface viables, and, in aseptic filling areas, personnel. Procedures should address frequencies and locations for monitoring, alert and action limits for each area, and corrective action 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 expected in areas in which upstream steps are performed, e.g., extraction and clarification. These operations are usually done in Class 100K or Class 10K areas, but may be performed in unclassified/controlled environments (ones with some level of particulate controls). As

the process moves further downstream, e.g., sterile filtration, more frequent monitoring is expected. Aseptic filling areas should be classified to a minimum of Class 100. Monitoring should be performed during production.

Determine that Class 100 conditions have been validated and are maintained in areas in which sterile product and components, including container/closure systems, are exposed.

If limits have been exceeded, ensure that an investigation was conducted and appropriate actions taken. Determine what action is taken with respect to products produced under out-of-limit conditions.

e. Buildings

Buildings should be appropriately constructed to prevent, reduce, and control potential contaminants and support the environmental control program. There should be sufficient space for manufacturing, receiving, packaging/labeling, storage, etc. The manufacturing areas should be designed to allow proper cleaning, maintenance, and other necessary operations.

If the facility processes spore-bearing organisms (i.e., molds), there must be distinct physical separation between the areas in which spore-bearing organisms are handled and other areas (see 21 CFR 600.11(e)(3)). This requires either a separate building or a part of a building that is physically separated from other parts, including having independent entrances and equipment solely for use with the spore-bearing organisms.

f. Water system

Water system diagrams should accurately reflect the current as-built conditions. While inspecting the system, look for dead legs and evidence of leaks and evaluate the location of drop points for sampling. All valves and connections should be of sanitary design.

Determine the source of the 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 are in place for maintenance, replacement, regeneration, and/or sanitizing water treatment components and that all instruments are routinely calibrated.

Review the firm's procedures and controls for the production, monitoring, and testing of all types of water used. Water quality should meet appropriate specifications and procedures should

include appropriate actions to take when action levels are exceeded.

g. Equipment

Equipment should be appropriately designed and placed to facilitate maintenance, adjustment, cleaning and use, and should be suitable for its intended use. Equipment should be validated, where appropriate.

The firm should have validated cleaning procedures, appropriate to the use of the equipment (i.e., multi-use vs. dedicated), which would include validation of removal of any detergents used. Records of equipment cleaning should be maintained.

Written equipment maintenance procedures/schedules should be readily available to the appropriate personnel. The firm should perform checks on a regular basis to ensure the maintenance schedules are followed and documented.

h. Reprocessing

If the firm reprocesses or reworks lots, there should be a written procedure for doing so. The decision to rework or reprocess should be documented, and should be done in accordance with established criteria. SOPs for reworking or reprocessing should be approved by CBER prior to implementation by the firm, and product that has been reprocessed or reworked cannot be distributed unless the reprocessing or reworking was done in accordance with an approved procedure. Determine if any lots were reprocessed or reworked.

i. Stability

Standardized allergenic extracts are subject to a stability determination. For those products that have recently been standardized, manufacturers may be performing stability studies as part of a license supplement. Once the original license commitment is fulfilled, manufacturers should have products on a routine stability program. Investigators should review the stability protocol for products on routine stability studies and determine if any products have failed to meet acceptance criteria.

If a manufacturer wants to extend an expiration date for a product, he must file a supplement with CBER. Alternatively, the manufacturer may file a stability protocol with CBER as a prior approval supplement. Ensure that the expiration date is the same as that in the approved application, approved supplement, or as listed in 21 CFR 610.53.

j. Records

Records required by GMP regulations must be maintained at the manufacturing facility or at another location reasonably accessible to responsible officials of the manufacturer and to FDA investigators. If the records are not maintained at the manufacturing facility, they must be made available in a reasonable amount of time. Other references in this program to record keeping may be found in equipment, stability, and testing sections.

i. Master Production and Control Record

The master production record contains the documentation necessary to produce a drug product.

The master production record for an allergenic product should include 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 in use in the manufacturing areas.

ii. Batch Records

A batch record must be generated for each individual lot of product. Verify that the batch records show the processes, tests, reworking/reprocessing the allergenic product went through from the beginning of manufacturing to distribution and reflect that all operations, processes, etc., described in the batch records were accomplished. Verify that batch records contain evidence that the labeling was examined prior to actual use.

k. Testing

Manufacturers must have established specifications and procedures for testing. Batch and release records should be reviewed to ensure that allergenic products met specifications prior to release for distribution. If the manufacturer performs any in-process testing, results from this should also be reviewed.

Unless specifically exempted, allergenic product manufacturers must comply with the testing requirements found in 21 CFR Part 610 and 680.

i. General safety and sterility

All allergenic products (standardized and non-standardized) are subject to the requirement to perform the general safety test and to meet sterility requirements. Exceptions to the testing required in 21 CFR 610.11 and 610.12 are found in 21 CFR 680.3(b) and (c).

ii. Potency and identity

Standardized allergenic products must be subject to potency and identity testing; these tests are not required for non-standardized allergenic products.

iii. Retesting

Retesting is allowed under defined conditions. If the manufacturer performs retesting, ensure that it has a procedure to determine when retesting is appropriate, how retesting should be performed (i.e., sample, how many repeats), and ensure the procedure is followed.

iv. Retention samples

The firm is required to maintain retention samples of each lot of product for the time prescribed in 21 CFR 211.170. Ensure that retention samples are available and are appropriately stored.

1. QA/QC

Manufacturers are required to establish a quality control unit that has the responsibility to approve or reject all components, packaging, drug products, labeling, etc. The quality control unit is also responsible for investigating errors in production records. Ensure that the facility has a quality control unit, determine the responsibilities of the quality control unit, and evaluate whether the quality control unit is effective in carrying out its responsibilities. Some allergenic product manufacturers are very small operations, so these firms may not have a separate QA/QC unit.

i. Personnel

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.

Ensure that employees are trained prior to performing a task.

If training is performed in-house, review the qualifications of the instructors and the process for evaluating the success of the training.

ii. Consultants

Consultants advising on any aspect of manufacturing must have sufficient training, education, and/or experience to advise on the subject for which they were retained. If the firm has a consultant for any aspect of manufacturing, evaluate the consultant's qualifications with regard to the area on which he/she is providing advise to the firm.

iii. Acceptance/rejection

Acceptance activities must be documented and be part of the batch record. If products are rejected, an evaluation should be performed to determine the cause of the problem.

The inspection and test status of product at all stages must be identified to ensure that only products which pass the required acceptance activities are distributed. This can include acceptable computerized identification or markings.

Acceptance criteria must be clearly identified. Records must show whether the product has passed or failed acceptance criteria.

Verify that the manufacturer has defined methods, e.g., inspections, tests, and other verification tools (certificates of analysis and supplier audits), to ensure that components, in-process product, and finished products conform to all specifications in the master production record prior to release for distribution and that acceptance activities are documented in the batch production record.

m. Deviations

i. Nonconforming product

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 during in-process or 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 defective products. Document and report on any distribution of out-of-specification products.

ii. Complaint handling

The firm must have and follow 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. The procedures must include a provision for assessing the complaint to determine if it should be reported as an adverse event.

All communications that meet the definition of a complaint should be treated as such, regardless of the manner in which they were communicated to the firm (e.g., service call). Complaints received orally (i.e., by phone) should be documented. All complaints should be reviewed and evaluated. Complaints should be investigated unless a similar complaint has been investigated and another investigation is not necessary.

Review and analyze complaints to identify existing and/or potential causes of nonconforming product or other quality problems. Be especially aware of complaints regarding product sensitivity and specificity which may subject products to recall. Determine if the firm has performed a sufficient complaint investigation.

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

iii. Reporting of errors & accidents

21 CFR 600.14(b) requires manufacturers of licensed allergenic products to promptly notify the Director, CBER, of errors or accidents in the manufacture of products that may affect their safety, purity, or potency.

Ensure all errors or accidents that were identified after the products were made available for distribution were reported to CBER. If confirmation of their submission to CBER is needed, contact CBER/TBLS.

iv. Adverse event reporting

21 CFR 600.80 requires that serious, unexpected adverse experiences associated with the use of a biological product in humans be reported to CBER 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 CBER as

required. If there are questions or concerns regarding the seriousness of, and therefore the reporting requirements for, an adverse event, contact CBER/TBLS.

n. 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 CBER; and that upon notification by the Director, CBER, a manufacturer shall not distribute a lot of a product until it is released by the Director. Standardized allergenic products are subject to CBER lot release testing; non-standardized allergenic products are not. The requirement for CBER lot release testing does not mean a manufacturer may perform less finished product testing before releasing a product for distribution.

For standardized allergenic products, review representative lot release test records to determine if lots were released for distribution prior to lot release by CBER. Compare raw test data against test results provided in protocols submitted to CBER to ensure that they correlate. Check whether any lot has failed to be released and if so, the reason for failure and the disposition of failed lots.

Some manufacturers of biological products have, through approved license supplements, received exemptions from lot release and are on a "surveillance" program; however, there are currently no allergenic product manufacturers on surveillance.

o. 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 biologics and drug 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. Manufacturers should also have a change control process, which should include review by a QA/QC component.

The type of notification required is based on the potential risk of the change to have an adverse effect on the safety or effectiveness of the product. Changes which have a minimal effect on the safety or effectiveness of a product may be implemented without being reported to CBER; however, manufacturers are required to include such changes in annual reports to the agency.

Data relevant to changes reported in annual reports (e.g., validation data) must be generated and should be reviewed as appropriate.

Changes with a moderate potential to have an adverse effect on the safety or effectiveness of a product may be implemented 30 days after receipt by FDA of a supplement, unless FDA informs the applicant that the change cannot be implemented until FDA reviews and approves the supplement.

Changes that have a substantial potential to adversely affect the safety or effectiveness of a product can not be implemented 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 CBER 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 CBER, and describe them in the inspection report. Determine if changes have been validated, when appropriate. If there is any question as to whether a change should have been reported, or whether a change should have been submitted in a supplement instead of an annual report, contact CBER/TBLS.

C. SAMPLE COLLECTION

CBER 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 Product Release Branch, Division of Manufacturing and Product Quality, (301 594-6517), for guidance prior to collecting samples.

Contact the CBER Sample Custodian (301 594-6517) before shipping any samples. All samples collected under this program will be shipped to:

Center for Biologics Evaluation and Research
Attention: Sample Custodian, HFM-235
5516 Nicholson Lane, Building B, Room 113
Kensington, MD 20895

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 or other applicable regulations on

the FDA-483, Inspectional Observations.

2. Notify DEIO and CBER/TBLS immediately if a potentially serious health hazard exists.
3. Report on all major areas or systems investigated 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.
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 CBER/TBLS (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.

Foreign inspections: The original EIR, endorsement, and exhibits should be sent to CBER/TBLS, regardless of classification, after the inspection is endorsed and reviewed in accordance with Team Biologics SOPs.

PART IV - ANALYTICAL

No field analyses are projected under this program.

Under the lot release program for licensed biologics [described in Part III.B.], CBER receives samples and test results for licensed allergenic products on a routine or quarterly basis. Therefore, routine sample collection under this program is unnecessary.

Any samples that are collected during an inspection (either CBER-requested or for cause) will be analyzed by CBER laboratories, e.g., Division of Manufacturing and Product Quality, HFM-207, or Division of Allergenic Products and Parasitology, HFM-410. See instructions for shipping in Part III.C.

Original results of analyses will be forwarded to the Core Team compliance officer, with a copy to the home district of the involved facility. Investigators should designate to whom the samples results should be forwarded on the FDA 464, Collection Report.

Copies of collection reports for physical samples must be submitted to CBER, Office of Compliance and Biologics Quality, Division of Case Management, HFM-610.

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 should be conducted using the procedures set forth in the Case Processing SOP established for Team Biologics/Core Team.

Regulatory/Administrative Follow-UpSignificant 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 allergenic products (Important: this list is not intended to be all inclusive):

1. Quality Assurance/Quality Control (21 CFR 211.22)
 - Product that did not meet release criteria was released for distribution and the firm had no data documenting evaluation for release.
 - Written procedures for production and process control are not drafted, reviewed, and approved by the appropriate organizational units and/or the quality control unit.
2. Personnel (21 CFR 600.10 and 211.25)
 - Personnel were not adequately trained in the particular operations the employees perform and in cGMP.
 - Personnel did not have the necessary education, training, and/or experience to perform their assigned functions.
3. Physical environment (21 CFR 600.11 and 211.42 - 211.58)
 - Separate or defined areas or other control systems were not established for manufacturing and processing operations to prevent contamination or mixups
 - Failure to establish an adequate system for cleaning and disinfecting the room and equipment.
 - Buildings are not maintained in a clean and sanitary condition.
 - Buildings are not maintained in a good state of repair.
 - Failure to provide a separate area for work with spore-bearing organisms to prevent contamination of other areas.
4. Equipment (21 CFR 211.63 - 211.72 and 600.11(b), (e))
 - Equipment used in the manufacture, processing, packing, or holding of a drug product is not appropriate for its intended use.

- Equipment is not cleaned, maintained, and sanitized to prevent malfunction or contamination.
- The cleaning process for equipment used to manufacture a drug product was not validated.
- Written procedures for cleaning and maintenance of equipment were not maintained or followed.
- Network software used in the manufacture of an allergenic product was not validated.
- Equipment is not routinely calibrated, inspected, or checked.
- Acceptance limits for equipment calibration are not established or followed.

5. Components, Containers and Closures (21 CFR 211.80 - 211.94 and 600.11(h))

- Written acceptance and rejection criteria for incoming components has not been established.
- Written procedures are not established and/or followed for the receipt, identification, storage, handling, sampling, and testing of components, drug product containers, and closures.
- Components and drug product containers are not handled in a manner to prevent contamination.
- Written standards or specifications, methods of testing, and methods of cleaning, sterilizing, and processing to remove pyrogenic properties are not established or followed.
- Components, drug product containers, or closures that are susceptible to microbiological contamination are not tested.

6. Source materials (21 CFR 680.1 and 601.22; Sections 351(a) and (b) of the PHS Act)

- Failure to maintain appropriate records.
- Testing or evaluation is not performed to verify the identity of each source material component.
- Testing is not performed on each source material component to demonstrate conformity with written specifications for purity, strength, and quality; or failure to (1) obtain a report of analyses from the source material supplier; (2) conduct at least one specific identity test on the source material; and (3) establish the reliability of the source material supplier's analysis through appropriate validation of the source material supplier's test results at appropriate intervals.
- There is no assurance that the source materials used contain no more than 1.0% of detectable foreign materials.
- There is no assurance that mold cultures are free of contaminating materials (including microorganisms) prior to harvest and that contamination is minimized during harvest and subsequent processing.
- The identity of mold seed cultures is not established.
- There is no documentation to demonstrate that the mold source material supplier had submitted and received approval of its mold standard operating procedures and test results.

- Failure to ensure that animals of the equine genus intended as source materials for allergenic products were treated to maintain immunity to tetanus.
- Failure to ensure that molds used as source materials are manufactured so that the source material will contain only the allergenic and other substances intended to be included in the final product.
- Each lot of source material is not identified with a unique lot number.

7. Production and Process controls (21 CFR 211.100 - 211.115 and 680.2)

- Written standard operating procedures for all aspects of product manufacturing are not established or followed.
- Manufacturing processes are not validated; appropriate validation protocols are not established; validation is not documented.
- Failure to ensure that all manufacturing steps are performed so that the product will contain only the allergenic and other substances intended to be included in the final product.
- Appropriate time limits for the completion of each phase of production to assure the quality of the drug product are not established.
- Specifications were not established for acceptable levels of contaminants.
- Processing control operations are not conducted so as to assure that the product conforms to applicable specifications.
- Manufacturer processed source material that did not comply with written specifications and manufacturer did not have an approved SOP to process non-compliance material.

8. Control of Microbiological Contamination & Environmental Monitoring (21 CFR 211.113(b) and 600.11)

- Written procedures designed to prevent microbiological contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization process are not established and/or followed
- Production and filling areas are not monitored for surface contaminants.
- The established system for monitoring environmental conditions is inadequate.
- The firm had no data to support the alert limits for particulate monitoring.
- The system used in the identification of environmental microbial isolates has not been challenged.
- Sterile media fills are not performed on a periodic basis.
- Personnel involved in aseptic processing are not monitored.

9. Testing (21 CFR 610.1, 211.165, 610.12, and 680.3(c))

- Finished product testing is not completed prior to release of products.

- Testing prescribed in the regulations is not performed.
 - Product was assigned an extended expiration date with no data to support the extended date.
10. Laboratory Controls (21 CFR 211.160 - 211.176, 680.3, 610.12, and 610.1)
- Failure to maintain laboratory controls that include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality, and purity.
 - Failure to establish an adequate program designed to assess the stability characteristics.
11. Records and Reports (21 CFR 600.12 and 211.180 - 211.198)
- Master production records failed to include all required information.
 - Complete records of each significant step in the manufacture and distribution are not maintained.
 - Labeling records did not reconcile with batch production records.
 - Records of the history of the manufacture or propagation of each lot of source material are not maintained.
 - Source materials are not clearly identified in the batch records.
 - The batch production record does not reflect the current manufacturing process.
12. Investigation/Production record review (21 CFR 211.192)
- Unexplained discrepancies in drug product production and control records or the failure of a batch to meet any of its specifications are not investigated and/or documented.
 - Final product sterility test failures are not investigated and/or documented.
 - The failure of a component to meet specifications is not investigated and/or documented.
 - The investigation of a product deviation failed to document all products potentially affected by the deviation.
 - There is no system to assure investigation of failed/rejected batches is documented.
 - Failures in sterility testing and/or environmental monitoring are not investigated and/or documented.
13. Complaint files (21 CFR 211.198)
- The complaint handling program is not established and/or not adequate.
 - Corrective actions are not taken to correct deficiencies in manufacturing processes found during complaint investigations.

14. Adverse Experience Reporting (AER) (21 CFR 600.80)

- AERs are not submitted or reviewed as required.

15. Licensing (21 CFR 601.10-22)

- Significant manufacturing changes were not reported to or approved by CBER.
- Product is not manufactured as described in the approved license application.

NOTE: Consult CBER/TBLS before including licensing violations on an FDA Form 483 or in a regulatory action recommendation.

16. Reporting of Errors (21 CFR 600.14)

- Errors and accidents in the manufacture of allergenic products were not reported.

Regulatory Actions

A firm's written corrective action 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 and the most effective way to protect the consumer. Because the number of manufacturers of allergenic products is small, 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 the appropriate enforcement action. Available options include Warning Letter, rescinding lot release, license revocation and suspension, seizure, injunction, or prosecution.

Warning letters: CBER concurrence should be obtained for all Warning Letters issued under this program. This will be reevaluated after CBER gains some experience with the program.

PART VI - REFERENCES AND PROGRAM CONTACTSREFERENCES

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, 600, 601, 610, 680.
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, including Subchapter 130; Subchapter 200, sections 205.100, 210.100, 270.100; and Subchapter 400, section 480.100.
7. Compliance Program Guidance Manual, Program 7356.002, Drug Process Inspections; and Program 7356.002A, Sterile Drug Process Inspections.
8. Guidance on Alternatives to Lot Release for Licensed Biological Products, CBER, July 1993.
9. Guidance for Industry: Changes to an Approved Application: Biological Products, CBER, July 1997.
10. Guideline on General Principles of Process Validation, May 1987.
11. Guideline On Sterile Drug Products Produced by Aseptic Processing, Center for Drugs and Biologics and ORA, June 1987.
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 Inspections of Lyophilization of Parenterals, ORA/ORO/DFI, July 1993
16. Guide to Inspections of Bulk Pharmaceutical Chemicals, ORA/ORO/DFI, September 1991, as amended May 1994.
17. FDA Policy for the Regulation of Computer Products, CDRH.

18. Biosafety in Microbiological and Biomedical Laboratories, DHHS.
19. United States Pharmacopeia, <51> Antimicrobial Preservatives - Effectiveness, and <61> Microbial Limits Tests.
20. Team Biologics/Core Team Case Processing SOP, Operations Group, March 1998.
21. Draft Guidance for Industry on Testing Limits in Stability Protocols for Standardized Grass Pollen Extracts, CBER, 1997.
22. International Conference on Harmonization Guideline; Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, November 1995.

How to Obtain Copies of Documents

Many of the above documents may be obtained from the following sources:

1. Copies of many CBER documents may be obtained from CBER's FAX Information System by calling 301-827-1800 or 1-800-835-4709. The following lists may be requested to determine what documents are available and how to order them:

9999 Documents Available from the CBER FAX Information System.

9998 CBER FAX Information System - Documents Added in the Last 30 Days

9997 CBER FAX Information System - Recalls, Market Withdrawals, Safety Issues.

9901 Guidelines, Points to Consider, and Other Guidance Documents for Human Biological Products Available From CBER's Office of Communication, Training and Manufacturers Assistance.

9003 Guidelines Applicable to the Center for Drug Evaluation and Research (CDER).

2. A CBER Bounce-Back E-Mail list of documents available by e-mail (DOC_LIST@CBER.FDA.GOV) is also available.

PROGRAM CONTACTS

CBER

Questions regarding CBER policy or requests for assistance:

Team Biologics Liaison Staff, HFM-604
Office of Compliance and Biologics Quality, CBER

301 827-6191

Potential Regulatory Actions:

Division of Case Management, HFM-610
Office of Compliance and Biologics Quality, CBER
Steven Masiello, Director
301 827-6201

Recall Coordinator

Division of Inspections & Surveillance, HFM-650
Office of Compliance and Biologics Quality, CBER
Alice Godziemski
301 827-6220

Mailing Address for CBER Contacts:

1401 Rockville Pike, Suite 200N
Rockville, MD 20852

ORA/OE

Questions regarding ORA policy or requests for guidance, and Core Team contact:

Jon Hunt
DEIO Biologics Group, ORO, HFC-132
301-827-5658

Questions pertaining to recalls

Willie Bryant
Office of Enforcement, HFC-230
301-827-0429

Questions pertaining to compliance issues

Sandra Whetstone
Office of Enforcement, HFC-210
301-827-0391

PART VII - CENTER RESPONSIBILITIESInspection Profiles and Information

The Team Biologics Liaison Staff (TBLS), Office of Compliance and Biologics Quality (OCBQ), CBER, 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.

The TBLS 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

CBER/OCBQ will monitor this program and evaluate reports of inspections. Results of evaluations will be shared with the field, ORA/ORO, and interested CBER units.

CBER/OCBQ will also coordinate and/or prepare an annual review and evaluation of this compliance program.