

SUBJECT: Inspections of Licensed Viral Marker Test Kits		IMPLEMENTATION DATE April 1, 1998
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DATA REPORTING		
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57FY-	42008 - domestic GMP inspections 42008A - domestic pre-license inspections 42108 - foreign GMP inspections 42108A - foreign 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.

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PART I - BACKGROUND

Within the FDA, the Center for Biologics Evaluation and Research (CBER) has been designated as the lead Center for regulating in vitro diagnostic devices (IVDs) used in blood and plasma donor screening; second, more specific (confirmatory) clinical laboratory tests associated with blood banking practices and other process testing procedures; and the instrumentation and software designed to be used exclusively with the test kits (see Reference #5). Because these IVDs are used thousands of times a day to enhance the safety of blood and blood components, thorough scrutiny must be given to their manufacturing and their compliance with applicable regulations and standards.

This program will focus on the inspection of licensed viral marker test kits for both donor screening and confirmatory or second, more specific testing of blood and blood components for transfusion-transmitted disease, and their exclusive instrumentation and software.

The intent of this program is to provide uniform guidance to FDA Office of Regional Operations (ORA) and CBER personnel to evaluate the conditions under which licensed viral marker test kits and their associated instrumentation and software are manufactured, and to enforce the applicable requirements.

CBER Product Responsibilities

Under the Public Health Service Act (PHS Act), CBER licenses IVDs which are used for screening blood and plasma donors for retroviral or other infectious agents; determining donor suitability; or determining transfusion compatibility to ensure the safety of blood, blood products or analogous products. Licensed IVDs include viral marker test kits intended for use in testing blood and blood components for transfusion-transmitted diseases, for example, hepatitis viruses, human immunodeficiency viruses (HIV) and other retroviruses; Blood Grouping Reagents, Reagent Red Blood Cells, and Anti-Human Globulin used in detecting human blood group antigens or antibodies; and Limulus Amebocyte Lysate (LAL). CBER also licenses some of the components of these IVDs. The products may be manufactured from human or animal, monoclonal or recombinant origin, and may be final finished products or be marketed for further manufacturing use.

Because these IVDs contain a biological component and are used to ensure the safety of blood and blood products, they are subject to regulation as licensed biological products under the PHS Act. IVDs also fall within the definition of a device as found in Section 201(h) 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 Medical Device regulations (especially Part 809, In Vitro Diagnostic Products for Human Use; and Part 820, Quality System Regulation).

In addition to the licensing process, CBER also approves products

through the PMA/510(k) processes. Some IVD products have been developed for use exclusively with a specific test instrument or software, and CBER regulates the laboratory instrumentation and associated software provided by licensed IVD manufacturers for exclusive use with their test kits through the 510(k) or premarket application (PMA) processes. HIV in vitro tests not used in relation to blood bank practices but, for example, for patient diagnosis, monitoring, or prognosis, are also regulated by CBER under the medical device authorities through PMAs.

Licensed IVD products regulated by CBER are handled somewhat differently than devices regulated by CDRH. CBER-regulated IVDs are used to screen the nation's blood supply, and it is therefore especially important that they work as expected. Given this concern, it should be noted CBER places a higher priority on the oversight of these IVD devices than CDRH places on the IVDs under their jurisdiction. Because the blood screening test is an important layer of safety for the blood supply, inspections of these products are comprehensive. Inspections of the facilities should not be preannounced if the firm manufactures only CBER-regulated products.

Technology

Assays used to detect blood borne pathogens are based on antibody or nucleic acid binding to their specific antigen or complementary nucleic acid sequence, respectively. These assays usually employ very specific biologically derived proteins, e.g., viral antigens or antibodies isolated from human or animal sources, or biotechnologically derived proteins or peptides, e.g., recombinant proteins or synthetic peptide sequences, and monoclonal antibodies. These components are derived from humans or animals directly or cultivated using biotechnology techniques. These active components are purified by typical procedures such as centrifugation, chromatography, or filtration, and are chemically conjugated to chromogens or isotopes for colorimetric or radiometric quantitation, e.g., enzyme conjugates, isotope labeled antigens or antibodies. In addition, complementary binding components, e.g., an antigen for an antibody or a "plus" nucleic acid sequence for a "minus" strand, can also be bound to a "solid phase," e.g., plastic bead, iron-magnetic particle, paddle, or microwell. The finished test kits may consist of all or some of the following components: coated beads, microwell plates, microscope slides, latex particles, or strips; conjugate enzyme or radioactive tracer; chromogens [o-Phenylenediamine · 2HCl (OPD), tetramethylbenzidine (TMB)]; calibrators; positive and negative control reagents; specimen diluent; wash buffers (for the solid phase); and stop solutions, which are chemical reagents such as sulfuric acid (H₂SO₄), used to stop the reaction. Human serum or plasma, negative for the disease marker, is used to prepare negative controls and, when dosed with the disease marker of interest, positive controls.

Screening test kits, e.g., Radioimmunoassay (RIA), Enzyme Immunoassay (EIA), Enzyme-Linked Immunosorbent Assay (ELISA), Strip Immunoblot Assay (SIA), and Microparticle Enzyme Immunoassay (MEIA) are qualitative, in that the results are non-reactive (negative) or reactive (positive), or, in the SIA, positive, negative or indeterminate. Confirmatory, or

second, more specific tests distinguish between false positive and true positive screening test results. Confirmatory test kits for HBsAg and HIVAg neutralize repeatedly reactive specimens, whereas Western blots and Recombinant Immunoblot Assays (RIBAs) distinguish reactivity to specific viral proteins.

Team Biologics

Until the mid 1990s, most licensed IVD 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 April 1998, and the inspections will be organized in accordance with the procedures developed by the Core Team under the Team Biologics program. The Core Team will also be primarily responsible for handling any enforcement actions that result from inspections performed under this program. The Core Team will ensure that the home district will be 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 licensed viral marker test kits 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 device GMP regulations (21 CFR Part 820), In Vitro Diagnostic Device regulations (21 CFR Part 809), and Biologics regulations (21 CFR Part 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 licensed viral marker test kits, their exclusive instrumentation and software.

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 viral marker test kits and licensed component manufacturers, their exclusive instrumentation and software.

Workplanning for these inspections will be coordinated by the Core Team. Each licensed IVD manufacturing facility 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.

This program is to be followed in conjunction with applicable sections of Compliance Program 7382.830 (Inspection of Medical Device Manufacturers).

At this time, inspections of licensed medical device manufacturers are not subject to the inspection initiatives developed by ORA and CDRH, as

outlined in the "Medical Device Industry Initiative" document. The Agency is evaluating whether the device inspection initiatives should be applied to all FDA-regulated facilities. At the time that these inspection initiatives are made applicable to other FDA-regulated industries, notification of wider implementation of the initiatives will be published in the Federal Register.

The design phase of a licensed IVD is one of the most important phases in its life cycle and is usually a part of the license application. While observations relating to departures from 21 CFR 820.30, Design Controls, are not to be included on FDA 483s until June 1, 1998, any change in the design or manufacture of a licensed IVD is subject to the provisions of 21 CFR 601.12 (See Part III, B.1.d), and deviations from this regulation should be included on the FDA 483. Investigators should complete the Design Control Inspection Strategy Report (February 1998 version), as described in Compliance Program 7382.830, during inspections under this program.

When performing inspections of licensed component manufacturers, in cases where the facility does not manufacture the complete kit, investigators should apply the general biologics regulations found in 21 CFR Part 600 and the standards set forth in the applicable licenses. In accordance with the QS regulation, investigators should not inspect these component manufacturers using the regulations found in 21 CFR Part 820.

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 Program 7382.830, Inspection of Medical Device Manufacturers, Part III; Guide to Inspections of Medical Device Manufacturers; Guideline for the Manufacture of In Vitro Diagnostic Products; Chapter 5 of the Investigations Operations Manual; guidance applicable to the manufacture of sterile and microbiologically controlled in vitro diagnostic products/medical devices; 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 licensed products.

Licensed viral marker test kits are subject to the regulations in 21 CFR Parts 600-660, in addition to the regulations and standards in Parts 803, 809, and 820. Licensed IVD 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/TBLS for assistance. Labeling requirements for instruments are found in 21 CFR Part 801.

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

Investigators should refer to the applicable parts of Compliance Program 7382.830, Inspection of Medical Device Manufacturers, for instructions when inspecting manufacturers of exclusive instrumentation and software for use with licensed IVDs.

B. INSPECTION1. Areas Specific to Licensed Viral Marker Test Kitsa. Test Kit Components (Raw Materials)

Determine the types of source materials used and their suppliers.

IVD 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 audits of the supplier. Unlicensed component manufacturers will not routinely be inspected.

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;
- 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;
- the firm has records of acceptable suppliers.

All viral marker test kit components manufactured by the licensed manufacturer of a finished product must be manufactured in accordance with the Medical Device GMP as well as licensing standards.

Licensed components not manufactured by the finished device manufacturer are not subject to regulation under 21 CFR Part 820, but are required to comply with the applicable regulations in 21 CFR Parts 600-660. The licensed components must also be manufactured in accordance with the approved license application.

The primary source material used in the production of many licensed viral test kits is human or animal blood, plasma, serum, or protein-rich fluids containing specific antigens or antibodies.

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.

Unlicensed recovered plasma or serum, if used as source material for licensed viral marker test kits, must be provided under a valid short supply agreement in effect with each supplier (see 21 CFR 601.22). Short supply is the only way in which unlicensed plasma or serum may be shipped for use in a licensed product. The short supply agreement should include

the manufacturer's acceptance criteria for the source material, e.g., storage/shipping temperatures, viral and blood group testing, and the like, and adherence to these conditions should be confirmed during the inspection.

Recombinant derived protein, monoclonal antibody, or pathogen specific nucleic acid sequence components may be purchased, rather than manufactured by the final kit manufacturer. The firm that manufactures these components must also be licensed, and must comply with the standards established in an approved license application and applicable sections of 21 CFR Subchapter F - Biologics.

All components contained in the test kit or used to manufacture the test kit should be adequately characterized to develop meaningful acceptance criteria for successful routine production. Major raw materials, e.g., diluent sera and proteins, chromogens, and conjugation chemicals, need to be further qualified beyond basic vendor specifications prior to their incorporation into the product. Critical raw materials, e.g., antibodies, antigens, and enzymes, need specific analysis and processing since they can have a major impact on the assay performance.

Bioburden alert and action levels should be established for raw materials capable of contaminating the final product or promoting microbiological growth.

Minimal qualification testing may be conducted on some routine components for which the manufacturer has documented that acceptance criteria are very broad and the likelihood of failure is relatively low.

1) Specific Components

a) Process Water

Water used in manufacturing processes and products must meet the minimum standards of Purified Water, as defined in the U.S. Pharmacopeia. Purified Water may be manufactured by distillation, ion exchange treatment, reverse osmosis, or other suitable process and should be prepared from water complying with EPA drinking (potable) water standards.

Ensure that the manufacturer has established microbial specifications and a monitoring program to include identification of the types of microorganisms present.

b) Chemicals

i) Inorganic Chemicals

Ensure that the vendor's certificate provided for routine components is reviewed by the manufacturer, e.g., those

that have been used for a long time or have known performance history.

Verify that for chemicals that pose a hazard, are unstable, or have unique performance characteristics, the manufacturer undertakes sufficient steps to assure the components meet license requirements.

ii) Biochemicals

Antibodies

Extensive qualification testing is usually necessary to ensure that all lots are produced consistently.

Antigens

Antigens may be serum derived, recombinant DNA (rDNA), synthetic or cell line derived proteins. Antigens used must be from a licensed manufacturer.

Review manufacturing SOPs and batch records for a representative number of lots to ensure that acceptance criteria are met.

2) Coupling Reactions

a) Solid Phase

Solid phase components, e.g., plates, beads, filters, and latex particles, often require special processing due to an inherent inability to filter out contaminants.

Ensure that:

- microbiological monitoring and control efforts are exercised throughout the entire process when handling, filling solutions and incubating for binding are performed,
- solid phase components are processed under HEPA filtered air conditions (a minimum of class 100,000 or preferably class 10,000) when possible, and
- actual filling or contact with coating solutions is performed in a critical area (class 100 environment) if the coating solution is sensitive to micro contamination.

For microwell plates, it is imperative that each well of each plate be coated uniformly since the initial binding reaction takes place on the inside surface of the microwell. There should be a system capable of verifying that each well is filled according to specifications.

Bead-grinding procedures prepare bead surfaces for the coating solution. Established specifications must be met.

Observe the on-going bead/plate/strip coating and filling operations if possible. Determine whether solid phase components and processes are controlled and characterized for chemical composition of the solid phase, reproducibility and optimization of the coating, uniformity and quantitation of coated antigen or antibody, contamination (bioburden, particulate and mold release), non-specific binding, preservative effectiveness, bioburden/sterility, stability, and packaging considerations.

b) Conjugation

Adjustments of conjugates are inherent in the manufacture of IVDs. Since it is unlikely that the exact dilution will be obtained every time, each lot of conjugate is compared to an approved reference lot, and dilutions are made until specifications have been achieved. An approved SOP must be in place for this adjustment. Typically, there should be no more than a 10% adjustment, and no more than 3 adjustments per lot without an investigation.

If more than three adjustments are made to any one lot, copy records showing the adjustments, as well as any written instructions and/or justification for them and any investigation conducted, and include them in the inspection report.

3) Ancillary Components

Review the manufacturing SOPs and batch records for a representative number of lots to ensure that acceptance criteria are met for test kit controls; diluents, buffers, chromogens, stopping reagents and other reagents; and containers, closures, and packaging.

b. Lot Release

Because the biological origin of most viral marker test kits makes them less suited to standardization by chemical or physical means, they must be tested in relation to standard reference preparations established and distributed to manufacturers by CBER.

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.

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 CBER at specified intervals, but they may market their products without receiving lot release. Some licensed viral marker test kits are on surveillance. If a regulatory action is taken against a viral marker test kit manufacturer, its product(s) may be removed from surveillance status. See Part VI, REFERENCES, #10.

Review representative lot release test records, especially for those products on surveillance, to ensure that all specifications have been met. 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.

c. Reporting of Errors

21 CFR 600.14(b) requires manufacturers of licensed IVDs and unlicensed IVD products required to be registered under 21 CFR Part 607 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 occurred were reported to CBER. If confirmation of their submission to CBER is needed, contact ITF.

See section B.2.1 (Medical Device Reporting) for additional reporting requirements.

d. 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 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.

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 CBER; however, manufacturers are required to include such changes in annual reports to the agency.

Data relevant to changes reported in annual reports (ie.

validation data) must be generated and made available during FDA inspections.

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.

See Part VI, REFERENCES, #4 and #11.

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 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 the ITF.

e. Labeling/Packaging

Labeling requirements applicable to licensed IVDs are found in 21 CFR 809, 820.120 and 820.130, as well as various sections of Parts 610 and 660. Labeling requirements for instruments are found in 21 CFR Part 801, 820.120, and 820.130. Specific wording for labeling is reviewed and approved by CBER.

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

2. Systems

The Medical Devices; Current Good Manufacturing Practice (CGMP); Quality System Regulation became effective June 1, 1997. Investigators should pay particular attention to the following aspects of the device GMP during inspections of licensed viral marker test kits and their instrumentation and software:

a. Complaint Files

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 Medical Device Reporting (MDR) reportable events. Ensure that such complaints are placed in a separate portion of the complaint file or otherwise clearly identified, and determine if the appropriate reports were filed with FDA. (Refer to section B.2.1). Complaints concerning death, serious injury or malfunction must be reported to FDA under the Medical Device Reporting regulations.

Ensure that the firm has written procedures for processing complaints involving the possible failure of a device, labeling, or packaging to meet performance specifications. The complaint file must contain all complaints including those that are open or still under investigation.

Review complaints received since the last inspection or June 1, 1997, whichever is later. Determine what files are maintained that meet the definition of a complaint [21 CFR 820.3(b)]. Ensure that all communications involving product deficiencies that meet the definition of a complaint for both viral marker test kits and their associated instrumentation 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. 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.

Manufacturers must have SOPs for determining whether complaints and other sources of data indicate a recurring quality problem. Review these SOPs and determine how the firm uses the data generated during these reviews. (See also section B.2.m.)

b. Quality System

The quality system is designed to prevent the design or production of nonconforming product and to identify, recommend, or provide solutions for quality problems and to verify their

implementation. The responsibility for activities affecting quality must be established in the firm's organizational structure.

Determine that there is an established, written and implemented quality system tailored to the viral marker test kits and their associated instrumentation that assures that the finished devices, the design process, the manufacturing processes, and all related procedures conform to approved specifications; and that all activities assure that products are controlled and adequate for their intended use, documentation is controlled and maintained, and equipment is calibrated, inspected, tested, etc.

1) Quality Audits

Quality audit procedures consisting of a formal, planned check of all elements in the quality system must be established and conducted to determine the effectiveness of the quality system. Independent inspections, performed on a periodic basis by appropriately trained individuals, and documented in audit reports, are to be made and the reports reviewed by management having the responsibility for the matters audited. It is recommended that the time between audits not exceed 12 months.

Determine whether the manufacturer has formal written procedures for conducting, reporting, and reviewing quality audits of all elements in the quality system, and how often audits are conducted. If it is possible to interview an auditor, obtain as much information as possible from him/her as to how the audits are performed, what documents are reviewed, how long audits take, etc. Determine if corrective action is taken by upper management when necessary.

FDA policy states that reports of internal or management audits will not be reviewed during inspections; however, investigators may request SOPs or schedules for performing these audits. Investigators may also review audit and evaluation procedures and documents that show conformance with purchasing control (21 CFR 820.50) and management review [21 CFR 820.20(3)(c)] requirements.

2) 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.

c. Design Controls

For licensed viral marker test kits, review and evaluate the processes, the methods, and the procedures established for design controls for conformance with standards and specifications in the license application. Cite deviations from these standards on the FDA 483.

For instruments and software used with viral marker test kits, review and evaluate procedures established for design controls after June 1, 1997. Until June 1, 1998, list any observations relating to design control inadequacies on a Design Control Inspectional Strategy Report. Refer to Compliance Program 7382.830, Attachment F, for instructions on completing the form. Note any concerns relating to the adequacy, safety, or efficacy of a particular instrument design in the inspection report and flag for review by CBER/ITF. Prior to June 1, 1998, do not collect documents or records related to these concerns. Beginning June 1, 1998, design control deviations may be placed on the FDA Form 483.

Determine whether procedures have been established and maintained for validating the device design and whether they have been appropriately performed under actual or simulated use conditions and documented.

Determine if procedures are established and maintained to ensure that the device design is correctly translated into production specifications and that a design history file (DHF) is established for each type of device which demonstrates that the design was developed in accordance with an approved plan. Ensure that any design changes are appropriately made.

d. Purchasing Controls

The device GMP does not apply to manufacturers of components or parts of finished devices unless they are manufactured by the finished device manufacturer; however, many components of licensed IVDs are regulated through the licensing process. Licensed components may not be purchased for use in a licensed test kit without prior CBER approval. Manufacturers must have procedures to ensure that all purchased or otherwise received products and services conform to their specified requirements. Investigators may review the procedures for audits of suppliers, but should not to review actual results.

Ensure that suppliers, contractors, and "sister" facilities or other corporate or financial affiliates providing components are appropriately assessed and selected, requirements are clearly and unambiguously specified, and only suppliers and

contractors that meet specifications are used.

Determine that procedures clearly define the type and extent of control that the manufacturer will exercise over suppliers and contractors. Assessment criteria should be documented and include a description of how the assessment was made.

Determine whether the manufacturer is or may be producing nonconforming devices using nonconforming components.

e. Production and Process Controls

Verify that specifications and documented work instructions are provided for all processes in which variations could result in the failure of a finished device to meet specifications. Verify that essential operations are noted in the Device History Record (DHR) with appropriate verification procedures. Ensure that the manufacturer develops, conducts, controls, and monitors production processes to ensure that the device conforms to specifications; and that the controls necessary to ensure conformance are described.

1) Production and Process Changes

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

2) Environmental Control

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.

Ensure that there are documented inspections of environmental controls that indicate that the systems are functioning properly.

Review microbiological test results for air, water, and surfaces to determine how well the environment is being controlled.

3) Personnel

Verify that personnel in contact with devices or their environment are clean, healthy, and suitably attired when working under conditions that could be reasonably expected to have an adverse effect on product quality.

4) Contamination Control

Licensed IVDs and their components, which if compromised can affect assay results, are required through the licensing process to pass the sterility test or have an equivalent method of microbiological control. Such control is accomplished both by bioburden monitoring and aseptic processing of test kit reagents. Exemptions from the sterility test requirements have been granted to manufacturers who have proven that such tests are not required for the maintenance of safety or purity [21 CFR 610.12(g)(4)] and/or the IVD's dating period is so short as to make sterility testing impractical.

Microbiologically controlled IVDs must be processed in a controlled environment throughout the process and have specified action and alert limits for which the firm can provide a meaningful rationale.

Regardless of the process used, it should be defined in terms of the desired results and allowable operating parameters which should be translated into written process specifications and maintained in the device master record.

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;
- 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; and
- the air handling system is sufficient to contain large volumes of infectious materials where appropriate, e.g., HEPA filtered air shower to protect the product and the environment.

5) Buildings

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.

Pay particular attention to areas or rooms that may be of

concern for particular operations, e.g., segregation of pre- and post-viral inactivation material and operations.

6) Equipment

Verify that:

- equipment is appropriately designed and placed to facilitate maintenance, adjustment, cleaning and use;
- equipment meets requirements to ensure its proper functioning for the manufacture of devices;
- equipment is validated;
- multi-use equipment has validated cleaning procedures to prevent carry-over;
- cleaning efficacy of dedicated equipment is confirmed;
- removal of detergents, if used in cleaning, is validated;
- where equipment maintenance is necessary, written maintenance procedures/schedules are posted on or near the equipment to be maintained or are otherwise readily available to the appropriate personnel;
- periodic inspections are performed per written procedures to assure that maintenance schedules are adhered to; and
- SOPs for operating the equipment are readily available to the personnel performing the operations.

7) Automated Processes

Ensure that software for computers or automated data processing systems that are part of the production or quality system are validated to adequately ensure their performance.

8) Inspection, Measuring, and Test Equipment

Verify that:

- the manufacturer has assured that all inspection, measuring, and test equipment is suitable for its intended use and capable of producing valid results;
- automated equipment and software is routinely checked, calibrated, and inspected according to written procedures and documented as having been done.
- calibration procedures include specific directions and limits for accuracy and precision, and provisions for remedial action;
- maintenance procedures for inspection, measurement, and test equipment are in effect;
- calibration records are displayed on or near each piece of equipment or are readily available to users and calibrators of the equipment.

9) Process Validation

Verify that:

- the validation program is planned and documented and all necessary parameters are included in the processing procedures;
- adequate validation of the manufacturing process has been

- performed; and
- validation is documented and maintained.

f. Acceptance Activities

Acceptance activities must be documented and be part of the Device History Record (DHR).

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.

Records must show whether the product has passed or failed acceptance criteria.

IVDs manufactured under controlled conditions are required to pass the USP 51 test, Antimicrobial Preservatives - Effectiveness.

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 Device Master Record (DMR) prior to release for distribution and that acceptance activities are documented in the DHR.

g. Nonconforming Product

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.

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 device inspection for failing to meet any or all of the product's specifications.

Audit all 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.

Determine whether the manufacturer has established and maintains procedures for reworking/reprocessing. SOPs for reworking/reprocessing should be approved by CBER prior to

implementation by the firm.

Examine records to see if any lots that have failed specifications were reworked or reprocessed, and if the manufacturer has determined whether reworking/reprocessing will have any adverse effects on the product.

Determine whether all sampling plans for inspection are based on acceptable statistical rationale and technique.

h. Corrective and Preventive Action

Verify that there are established procedures for implementing corrective and preventive action.

Review records of investigations to identify failure trends; compare trends and corrective action documentation.

Note continued distribution of devices with a known problem on the FDA 483 (or DCIS report for design problems).

Determine whether the firm's device design and/or process changes are or may be contributing to defective products. If changes have been made to the device design or manufacturing process, determine whether they have been validated.

i. Handling, Storage, Distribution, and Installation

Verify that the firm has written procedures to ensure that mixups, damage, deterioration, contamination or other adverse effects do not occur during handling and storage, and to ensure that only devices approved for release are distributed.

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 of devices shipped, date shipped, and control/lot numbers used.

j. Records

Records required by Quality System (QS) Regulations/cGMP requirements must be maintained at the manufacturing facility or at another location reasonably accessible to responsible officials of the manufacturer and to FDA investigators.

1) Device Master Record (DMR)

The DMR contains the documentation necessary to produce a device.

The DMR for IVDs should have written processing procedures and contain a manufacturing section dealing with areas such as solution preparation and filling; status records for weighing, mixing, filling, etc., used for the general control of IVD products.

The DMR for instruments is expected to contain device specifications and drawings; procedures and instructions for production, installation, maintenance and servicing; data forms; and test/inspection reports.

Ensure that the DMR contains or references the procedures and specifications that are current on the manufacturing floor and that there is a formal method for approving and making changes to the DMR.

2) Device History Record (DHR)

Verify that DHRs representing individual lots or devices exist for all finished devices manufactured, showing the processes, tests, reworking/reprocessing the device went through from the beginning of manufacturing to distribution and reflecting that all operations, processes, etc., described in the DMR have been accomplished.

Ensure that viral marker test kits are assigned control/lot numbers for traceability, in accordance with 21 CFR 809.10.

Verify that history records contain evidence that the labeling was examined prior to actual use and labeling reconciliation is performed.

3) Quality System Record (QSR)

Ensure that the QSR includes or makes reference to the location of procedures and documentation required by the QS regulations.

4) Stability Records

Stability records are required to support labeled dating periods. Ensure that stability records show that the final test kits and their individual components have been 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 test kit samples and performs testing, where appropriate, for the entire dating period.

k. Servicing

Check whether manufacturers of instruments sold for exclusive use with viral marker test kits have a system in place to analyze service reports to identify causes of nonconforming product and to screen repair and service requests to determine whether any meet the definition of a complaint.

l. Medical Device Reporting (MDR)

Each event requiring the firm to submit an MDR is to be documented in an MDR event file, and the files are to be accessible to FDA personnel for review and evaluation.

Determine whether the manufacturer has developed, maintained, and implemented written MDR procedures in accordance with 21 CFR Part 803. Ensure that MDRs are filed within the time frames required by the regulations.

m. Corrections and Removals/Recalls

After May 18, 1998, device manufacturers are required to report any corrections or removals of a product made to reduce a risk to health (the equivalent of a Class I or II recall) to FDA within 10 working days of initiating such correction or removal (21 CFR 806). Determine whether corrections and removals not reported to FDA were properly classified as Class III recalls. NOTE: No report of a correction or removal is required under 21 CFR 806 if the correction or removal was submitted as an MDR.

In the event of the recall of a viral marker test kit, contact the CBER recall coordinator to determine whether a subsequent recall of blood or blood components tested with the product and/or a health hazard assessment may be necessary.

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 Product Quality Control, (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, MDR, or other applicable regulations on the FDA Form 483, Inspectional Observations, with the exception of design control deviations occurring between June 1, 1997 and May 31, 1998 (unless they can be linked to changes from standards in an approved license application, as described in section B.2.c). See Program 7382.830, Part V, and Attachment F, for Design Control Inspectional Strategy. Observations for failure to have a 510(k) or PMA or for licensing issues should not be placed on the Form 483 without first checking with CBER/ITF.
2. Notify DEIO and CBER/ITF 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 and applicable sections of PART III of Program 7382.830, 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. Obtain copies of specifications and/or SOPs that are regarded as inadequate and explain in the report why this conclusion was reached. Actual operations should be observed to determine if they are as described in SOPs.
5. 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.
6. Domestic inspections: Send a copy of each establishment inspection report, including endorsement and classification, to CBER/ITF (see Part VI, Program Contacts). For NAI and VAI inspections, 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/ITF, regardless of classification.

PART IV - ANALYTICAL

No field analyses are projected under this program.

Under the lot release program for licensed biologics [described in Part III.B.1.b)], CBER receives samples and test results for licensed in vitro diagnostics (IVDs) 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-670, or Division of Transfusion Transmitted Diseases, HFM-310. 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, Division of Case Management, HFM-610.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

Viral marker test kits are vitally important in establishing the safety of blood and blood products. Any significant deficiency in their manufacture has potentially far-reaching consequences. 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-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 licensed IVDs and/or their exclusive instrumentation or software (this list is not intended to be all inclusive):

1. Design controls (For instruments and software, 21 CFR 820.30, beginning June 1, 1998; and for licensed IVDs, 21 CFR 601.20, 601.12)
 - a. Written manufacturing specifications are not established, implemented, or controlled.
 - b. Device specification changes are not subjected to sufficiently stringent controls.
 - c. Inadequate change control.
2. Complaint files (21 CFR 820.198)
 - a. Complaint handling program is not established and/or not adequate.
 - b. Device failures are not adequately investigated or documented.
 - c. Corrective actions are not taken to correct deficiencies in manufacturing processes found during complaint investigations.
3. Quality System Requirements (21 CFR 820.20-820.25)
 - a. Quality assurance program and audit procedures are inadequate and/or not established or documented.
 - b. Personnel lack necessary training, or training system is not established or adequate.

4. Production and Process Controls (21 CFR 820.70-820.75)
- a. Production and process control procedures are not established, maintained, and/or followed.
 - b. Formal approval process for changes in the manufacturing process are not established and/or maintained; changes are not validated.
 - c. Personnel in contact with a device during the manufacturing process are not clean, healthy, or suitably attired.
 - d. Equipment is not routinely calibrated, inspected, and checked in accordance with written procedures; records are not kept to indicate that procedures were performed as required; and/or equipment is not suitable for its intended purposes.
 - e. Procedures are not established for specification control measures to assure that the design basis for the device and components is correctly translated into approved specifications, e.g.:
 - 1) Manufacturing processes, including adjustments and/or dilutions are not validated.
 - 2) Sampling plans lack sufficient specific information by which to evaluate the performance of a process.
 - 3) Upper or lower limits are not defined.
 - f. Processing control operations are not conducted so as to assure that the device conforms to applicable specifications.
 - g. Appropriate validation protocols are not established; validation is not documented.
5. Acceptance Activities (21 CFR 820.80-820.86)
- Appropriate written procedures for acceptance of components are not established.
6. Records (21 CFR 820.180-820.186 and 600.12)
- a. Complete device master records are not maintained.
 - b. Device history records are not maintained.
 - c. Records are not maintained concurrently with each step in the manufacture and distribution of a licensed IVD.

7. Medical Device Reporting (MDR) (21 CFR Part 803)

MDRs are not submitted or events are not investigated as required.

8. Premarket Notification or Premarket Approval (21 CFR 807.81-807.100, 814)

Premarket notification or premarket approval application was not submitted as required for exclusive software and laboratory instrumentation.

NOTE: Confirm with CBER/TBLS before including on an FDA Form 483 or in a regulatory action recommendation.

9. Licensing (21 CFR 601.10-22)

- a. Significant changes were not reported to or approved by CBER.
- b. 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.

10. Reporting of Errors (21 CFR 600.14)

Errors and accidents in the manufacture of licensed IVDs, and of unlicensed IVDs required to be registered under 21 CFR Part 607, are not reported.

11. Components (Sections 351(a) and (b) of the PHS Act, 21 CFR 601.22, and Section 502(a) of FD&C Act)

Source material is not licensed or not shipped under short supply provisions.

As a general rule, deviations in the areas of sterile filtration, filling, environmental monitoring, and water quality are also considered significant because all licensed viral marker test kits must be sterile or microbiologically controlled.

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. In cases in which expeditious regulatory or administrative action appears appropriate, contact CBER's Division of Case Management, HFM-610, immediately.

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 viral marker test kits 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 appropriate regulatory and/or administrative action.

Available options for regulatory actions include Warning Letter, license revocation and suspension, seizure, injunction, prosecution, civil money penalty, or order for repair, replacement or refund.

The Regulatory Procedures Manual should be used as a reference to assist in determining which regulatory action is appropriate. For additional assistance, the CBER/DCM may be contacted. When it is determined that a regulatory action may be appropriate, follow the current procedures outlined in the RPM and through Team Biologics/Core Team for guidance.

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, Section 211.166, and Parts 600, 601, 610, 660, 803, 806, 809, and 820.
4. 21 CFR Part 314 et al, Changes to An Approved Application, Final Rule, FR/Vol 62, #142/7/24/97 (39890 ff).
5. Intercenter Agreement Between The Center for Biologics Evaluation and Research and The Center for Devices and Radiological Health, 10/31/91.
6. Investigations Operations Manual (IOM).
7. Regulatory Procedures Manual (RPM), Chapter 4, Advisory Actions; Chapter 5, Administrative Actions; Chapter 6, Judicial Actions; and Chapter 10, Other Procedures.
8. Compliance Policy Guides, including Sub Chapter 130; sections 110.100, 205.100, and 210.100.
9. Compliance Program Guidance Manual, Program 7382.830, Inspection of Medical Device Manufacturers.
10. Guidance on Alternatives to Lot Release for Licensed Biological Products, CBER, July 1993.
11. Guidance for Industry: Changes to an Approved Application: Biological Products, CBER, July 1997.
12. Guidance on Quality Systems for the Design and Manufacture of Medical Devices, Issue 7, August 1994, Global Harmonization Task Force.
13. Guideline on General Principles of Process Validation, May 1987.
14. Guideline On Sterile Drug Products Produced by Aseptic Processing, CDB, CDRH, June 1987.
15. Guideline for the Manufacture of In Vitro Diagnostic Products, FDA, CDRH, OC, January 1994.
16. Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics, CDER, CBER.

17. Guide to Inspection of Medical Device Manufacturers, ORA/CDRH, June 1997.
18. Guide to Inspections of High Purity Water Systems, ORA/ORO, June 1993.
19. Points to Consider in the Manufacture of In Vitro Monoclonal Antibody Products Subject to Licensure, CBER.
20. Points to Consider for In Vitro Tests to Detect Antibodies to HIV-1, CBER.
21. Points to Consider in the Manufacture and Clinical Evaluation of In Vitro Test Kits for Detection of Antibodies to HIV Type 1, CBER.
22. Points to Consider in the Manufacture of Recombinant DNA Derived Products, Monoclonal Based In Vitro and In Vivo Products, CBER.
23. Medical Device Reporting for Manufacturers, CDRH, May 1997.
24. FDA Policy for the Regulation of Computer Products, CDRH.
25. Medical Device Quality Systems Manual: A Small Entity Compliance Guide, U.S. DHHS, FDA, CDRH, 1997
26. The FDA and Worldwide Quality Systems Requirements Guidebook for Medical Devices, compiled by Kimberly A. Trautman, 1997, ASQC Quality Press, Milwaukee, WI.
27. Biosafety in Microbiological and Biomedical Laboratories, DHHS.
28. United States Pharmacopeia, <51> Antimicrobial Preservatives - Effectiveness, and <61> Microbial Limits Tests.
29. Team Biologics/Core Team Case Processing SOP, Operations Group, March 1998.

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.
3. CDRH information may be obtained from CDRH Facts-On-Demand(F-O-D) by calling 301-827-0111 or 1-800-899-0381. For additional information on obtaining MDR documents from the CDRH F-O-D system, call CDRH F-O-D and request Shelf number 5799 from DSMA Facts.

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:

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 Inspection Task Force (ITF), Office of Compliance (OC), 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 ITF 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/OC 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/OC will also coordinate and/or prepare an annual review and evaluation of this compliance program.