Compliance Program Guidance Manual
Chapter – 42 Blood and Blood Products

Inspection of Licensed In-Vitro Diagnostic (IVD) Devices Regulated by CBER - 7342.008

Implementation Date: October 1, 2012 **Completion Date:** Ongoing

PRODUCT CODES:	PROGRAM/ASSIGNMENT CODES:
57V *In Vitro* Diagnostic Products 57Y *In Vivo* and *In Vitro* Diagnostic Products N.E.C.	42008F Level 1 Inspection – Licensed IVDs 42008G Level 2 Inspection – Licensed IVDs 42008A – Pre-license Inspection – IVDs 42832 – Pre-approval inspection – Biological Products

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FIELD REPORTING REQUIREMENTS

All original domestic and foreign Team Biologics (TB) Establishment Inspection Reports (EIRs) and exhibits will be sent via overnight mail delivery to the attention of the TB supervisor at:

US FDA
Office of Regulatory Affairs/ Office of Regional Operations
Division of Domestic Field Investigations
12420 Parklawn Drive, ELEM-2124
Rockville, MD 20857

The reports will be tracked by the Division of Domestic Field Investigations (DDFI) program specialist who will also perform an initial quality assurance review. DDFI will be responsible for distribution of the reports as appropriate for review and final classification.

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

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

Domestic Post-Market Inspections:

Notify CBER, Office of Compliance and Biologics Quality (OCBQ), Division of Inspections and Surveillance (DIS) HFM-650 at cberinspections@fda.hhs.gov when EIRs are available in Turbo EIR.

The signed original EIR is maintained by the home district regardless of classification. The ORA/OE Compliance Officer (CO) is responsible for releasing the EIR under Field Management Directive (FMD) 145. The home district is responsible for Freedom of Information Act (FOIA) requests for records related to the inspection.

Foreign Post-Market Inspections:

CBER acts as the "home district" for foreign inspections of CBER-regulated products. Send the signed original EIR, with exhibits, to OCBQ/DIS/HFM-650, regardless of recommended classification. CBER is responsible for releasing the EIR under FMD 145 and for FOIA requests for records related to the inspection.

Pre-license and Pre-approval Inspections

CBER/OCBQ's Division of Manufacturing and Product Quality (DMPQ) acts as the "home district" for all pre-license and pre-approval inspections of CBER-regulated products, with the exception of blood and blood components, whether foreign or domestic. The lead CBER inspector should: 1) send a copy of the signed original EIR and Form FDA 483 to OCBQ/DIS/HFM-650; and 2) include the complete original EIR, with exhibits, in the license application file documents as per current CBER standard operating procedures.

Inspection Level Reporting

The EIR narrative report's Summary section and the FACTS Inspection Result section (Endorsement Text Field) should include the inspection level and the major systems inspected for a level II inspection in addition to the information specified in the Investigations Operations Manual (IOM) Subchapter 5.10, Reporting.

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PART I - BACKGROUND

While most medical devices subject to Food and Drug Administration (FDA) oversight are regulated by the Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER) is also responsible for the regulation of certain medical devices.

Currently, CBER is designated the lead Center in FDA for regulating in vitro diagnostic (IVD) medical devices intended for screening or confirmatory clinical laboratory testing associated with blood banking practices and other process testing procedures. These IVD products include those required for screening of blood, blood products, human cells, tissues, and cellular and tissue-based products (HCT/Ps), supplemental testing, and related blood banking practices (such as blood typing and compatibility testing) and are licensed under Section 351 of the Public Health Service (PHS) Act. Examples of IVDs licensed by CBER include:

- Reagent Red Blood Cells
- Blood Grouping Reagents
- Donor screening tests (e.g., Human Immunodeficiency Virus (HIV) 1 and 2, Hepatitis B and C Virus)
- Anti-Human Globulin
- Limulus Amebocyte Lysate (LAL) test kits

These are examples of products subject to this compliance program (hereinafter referred to as "licensed IVDs").

In addition, CBER regulates devices which are not licensed, but are instead cleared or approved under the Federal Food, Drug, and Cosmetic (FD&C) Act's 510k or PMA provisions, and, as such, are not subject to this compliance program. Inspections of these devices should be performed in accordance with CDRH's Compliance Program 7382.845, Inspection of Medical Device Manufacturers.

Examples of devices regulated by CBER but not subject to this licensed IVD compliance program include:

- Plasmapheresis machines used to collect, process and/or administer a biological product
- Quality assurance reagents and 510(k) cleared instruments intended for use in conjunction with licensed IVDs
- Peripheral blood and umbilical cord blood stem cell collection kits
- Leukocyte typing sera
- Computer software with blood bank claims
- HIV test kits with only diagnostic claims
- Automated immunohematology analyzers

Licensed IVD products are subject to the applicable regulations promulgated under both the FD&C Act and PHS Act. These regulations include:

- 21 CFR Part 803 – Medical Device Reporting
- 21 CFR Part 806 – Reports of Corrections and Removals
- 21 CFR Part 809 – In Vitro Diagnostic Products for Human Use

- 21 CFR Part 820 – Quality System Regulation
- 21 CFR Part 600 – Biological Products: General
- 21 CFR Part 601 – Licensing
- 21 CFR Part 607 – Establishment Registration and Product Listing
- 21 CFR Part 610 – General Biological Products Standards
- 21 CFR Part 660 – Additional Standards for Diagnostic Substances for Laboratory Tests

The Quality System (QS) regulation at 21 CFR Part 820 sets forth the Current Good Manufacturing Practice (CGMP) requirements for licensed IVD products. The requirements in this part govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices for human use. The additional regulations and standards in 21 CFR Parts 600-660 applicable to licensed IVDs supplement the CGMP requirements and provide a comprehensive structure intended to ensure that licensed IVDs will be safe and effective and otherwise in compliance with the FD&C and PHS Acts.

Licensed IVD manufacturers must also comply with the commitments and applicable standards in their Biologics License Application (BLA). Licensed IVDs are of critical importance for maintaining a safe and effective supply of blood, blood products, and other biological products and in promoting and protecting public health. To help ensure that industry produces these products to be consistently safe, pure, potent, effective, and appropriately labeled, FDA conducts CGMP inspections of each establishment at least biennially. Pre-license inspections (PLI) for new biological products under review and pre-approval inspections (PAI) for significant changes to an approved BLA are performed to ensure compliance with the regulations prior to approval of a new license or significant change to the application, respectively.

Team Biologics (TB) leads routine biennial and compliance follow up CGMP inspections of licensed IVD manufacturers. TB represents a cooperative effort where ORA and CBER work together to support the program, using the investigative skills of ORA and the medical/scientific and product expertise of CBER, to promote and protect the public health through coordinated, integrated assessments of the compliance status of biological product manufacturers, including manufacturers of licensed IVDs. In most cases, CBER conducts the PLIs and PAIs, with CBER/OCBQ/DMPQ leading the inspections, and utilizing the CGMP and scientific expertise of CBER reviewers and review committee. TB investigators occasionally perform PLIs and PAIs.

This systems-based risk-management approach identifies major systems that are common to establishments manufacturing licensed IVD products. This program also establishes two levels of inspectional coverage to evaluate an establishment's compliance with applicable CGMP regulations; Level I (Full) – a comprehensive evaluation of the four major systems (Management Controls, Design Controls, Corrective and Preventive Action, and Production and Process Controls), and Level II (Abbreviated) – an evaluation of one mandatory major system (Corrective and Preventive Action), plus one additional major system (Design Controls or Production and Process Controls) on a rotating basis.

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

Continued biennial inspections under this compliance program will:

- Safeguard the public health by reducing the risk of adulterated or misbranded licensed IVD products reaching the marketplace;
- Increase communication between the industry and the Agency; and
- Provide timely feedback during inspections to improve manufacturers' compliance with CGMPs.

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

PART II- IMPLEMENTATION

A. OBJECTIVE

This compliance program replaces the previous compliance program for licensed viral marker test kits (7342.008) and represents a continuing compliance and surveillance activity conducted to ensure licensed IVDs are safe, pure, potent, effective, and appropriately labeled. Facility inspections are performed to:

- Ensure that manufacturers manufacture products that meet the standards described in applicable provisions of the regulations. These include regulations in 21 CFR Parts 600, 601, 610, and 660, and in 21 CFR Parts 803, 806, 809, and 820;
- Ensure that manufacturers meet any additional conditions of licensure in the approved BLA and/or supplements.
- Identify manufacturers who are not in compliance with the regulations.
- Bring manufacturers into compliance through voluntary, advisory, administrative and/or judicial means, as appropriate.

This compliance program provides inspectional instructions to investigators, inspectors, and product specialists assigned to perform biennial, for cause, PLI, and PAI inspections of manufacturers of CBER licensed IVD products, and provides administrative/regulatory strategy for the compliance officer (CO) and investigator. It includes information regarding noncompliance with applicable regulations, provides information necessary to evaluate overall operations, and ensures that appropriate compliance actions are initiated against those manufacturers found to be in significant noncompliance with applicable laws and regulations.

Firms covered under this compliance program include licensed manufacturers of:

- Blood and HCT/P donor screening and confirmatory test kits for communicable disease agents, and all licensed bulk manufacturers of such products
- Blood Grouping Reagents
- Reagent Red Blood Cells
- Anti-Human Globulin
- LAL test kits

B. STRATEGY

This compliance program outlines a systems-based, risk management approach to conducting a CGMP inspection. It identifies major systems in the establishment's operation for inspection. The inspection is a comprehensive evaluation of the critical areas in each system used by the establishment.

While the QS regulation can be grouped into seven systems, the following four systems are considered major systems and are the basic foundation of a firm's quality management system:

- **Management Controls** - the system that establishes quality policy, objectives, and procedures; provides adequate resources for device design, manufacturing, quality

assurance, distribution, installation, and servicing activities; also assures the quality system is functioning properly
- **Design Controls** - the system that controls the design process to assure that devices meet user needs, intended uses, and specified requirements
- **Corrective and Preventive Actions (CAPA)** - the system that collects and analyzes information, identifies and investigates product and quality problems, and takes appropriate and effective corrective and/or preventive action to prevent recurrence
- **Production and Process Controls (P&PC)** - the system that includes the measures and activities to control the manufacture of IVDs including following and documenting performance of approved manufacturing procedures

The three remaining systems (Facilities and Equipment Controls, Materials Controls, and Document/Records/Change Controls) cut across a firm's quality management system and are evaluated while covering the four major systems.

Medical Device Reporting, Corrections and Removals, and Biological Product Deviation Reporting requirements should be covered when covering the CAPA system.

The inspection of licensed IVD manufacturers is conducted under either a Level I (Full) or Level II (Abbreviated) inspection option.

- A **Level I (Full) inspection** is an in-depth inspection of the four major systems, and provides a comprehensive evaluation of the establishment's compliance with CGMP.
- A **Level II (Abbreviated) inspection** is a streamlined evaluation of an establishment's compliance with CGMP, and provides coverage of one mandatory major system, CAPA, plus at least one additional major system, either P&PC or Design Controls, on a rotating basis during successive biennial inspections. The Management Controls system should not be selected as the additional major system during a Level II inspection unless justified by issues identified during inspection planning or the inspection of the CAPA system.

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

C. PROGRAM MANAGEMENT INSTRUCTIONS

1. Frequency of CGMP Inspections

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

Exceptions:

This inspectional frequency does not apply to firms that meet any of the following conditions as unique inspectional frequencies may be established based on each firm type mentioned below:

- Firms under a Consent Decree of Permanent Injunction, that have varied inspection schedules specified by the terms of the consent decree
- Firms under a Notice of Intent to Revoke and/or other administrative actions

- Compliance follow-up inspections to verify a firm's implementation of corrective action subsequent to regulatory action
- A newly licensed facility

These firms are ordinarily inspected using the Level I (Full) Inspection Option.

2. Scheduling of Inspections and Assignment of Investigators

A. Routine post-marketing inspections:

- The TB supervisor (or designee) works with CBER/OCBQ to develop the work plan schedule of inspections, and to ensure CBER product specialist participation, either on-site or by consult, in CGMP inspections. All parties attempt to minimize rescheduling of inspections, but changes are at times necessary. The TB supervisor promptly notifies and consults with CBER regarding schedule changes.
- After reviewing the establishment's inspectional history and other relevant information, licensed IVD manufacturers will be scheduled for either a Level I (Full) or Level II (Abbreviated) inspection.
- Inspections will generally be conducted using a team approach with a TB investigator leading, and a CBER product specialist participating. The inspection team may include other ORA or CBER participants, as necessary, to ensure appropriate coverage of the facility being inspected. If CBER on-site participation is not possible, the TB investigator(s) will conduct the inspection with off-site participation (e.g., telephone) of the product specialist as needed.

B. Pre-license or pre-approval inspections:

CBER is responsible for the conduct of all PLI and PAI inspections of CBER-regulated products subject to licensure. These inspections (if deemed to be necessary) are led by CBER/OCBQ/DMPQ and are part of the managed review process of a BLA or supplement (for more information see SOPP 8410). CBER identifies the scope and content of the inspection and invites ORA to participate in the inspections. CBER/OCBQ/DMPQ will notify the district office and the TB supervisor of all pending pre-license or pre-approval inspections.

PART III - INSPECTIONAL

A. INSPECTIONAL PROCEDURES

Review and use the applicable sections of Chapter 5 of the Investigations Operations Manual (IOM); Compliance Program 7382.845, Inspection of Medical Device Manufacturers; the relevant regulations in 21 CFR Parts 600, 601, 610, 660, 803, 806, 809, and 820, and other guidance applicable to the manufacture of CBER regulated IVD products. If there are differences between the above referenced documents and the instructions in this program, investigators should follow the instructions in this program when conducting inspections.

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

In accordance with the QS regulation (21 CFR 820.1(a)), investigators should not inspect component manufacturers using the regulations found in 21 CFR Part 820. Component manufacturers are only inspected: 1) for cause; or 2) when the component manufacturer, who does not manufacture the finished IVD, is licensed and has an active BLA for the component. When such an inspection occurs, investigators should apply the general biologics regulations found in 21 CFR Parts 600, 601, 610, and 660, and the standards set forth in the applicable licenses.

The TB inspection team, including the appropriate product specialist, will develop the overall inspectional approach for individual CGMP inspections. Products needing special coverage will be addressed as part of the specific inspectional approach. A similar approach is applied to CBER PLIs and PAIs with CBER/OCBQ/DMPQ and the product specialist reviewer for the submission.

B. INSPECTIONAL COVERAGE

Inspections of licensed IVD products conducted under this compliance program will assess the firm's systems, methods, and procedures to ensure that the firm's quality management system is effectively established (defined, documented and implemented) and effectively maintained.

All inspections should include the assessment of post-market information on licensed IVD products to include:

- Review of recalls
- Review of MDRs (21 CFR Part 803). Be alert to the fact that MDRs may contain information on recalls that have not been reported through the district under 21 CFR Part 806.
- Review of corrections and removals (21 CFR Part 806)
- Review of Biological Product Deviation (BPD) Reports (21 CFR 600.14)
- Review of major and moderate changes (21 CFR 601.12(b) and (c)) in device specifications or in the manufacturing specifications
- Follow-up on previous Form FDA 483 observation(s), to include the corrections, corrective actions or preventive actions for the observation(s) and the related system(s)

Available post-market information should be reviewed as a part of the preparation for the inspection. See the Additional Inspectional Information found in Part III., Section E., for more instructions on post-market information.

Inspections of licensed IVDs should generally be conducted using the Quality System Inspection Technique (QSIT). Guidance for performing QSIT inspections is provided in the Guide to Inspections of Quality Systems, August 1999, also called the QSIT Guide. The QSIT tool can be scaled to meet the needs of each particular inspection.

As noted in the QSIT Guide, the QSIT approach to performing system inspections is based on a "top-down" approach. The system approach is designed to provide investigators with the key objectives that can help determine a firm's state of compliance. The "top-down" approach looks at the firm's overall level of control for addressing quality before actually looking at specific quality problems. In this approach, inspections complete the assessment of each system by sampling records, rather than beginning with records review and subsequently moving to procedures. The "top-down" approach begins each system review with an evaluation of whether the firm has addressed the basic requirements in that system by defining and documenting appropriate procedures. This is followed by an analysis of whether the firm has implemented the requirements of that system.

For each major system, the inspection should determine if the firm has defined and documented the requirements by reviewing procedures and policies, and then the inspection would move to a review of records, looking at raw data to determine if the firm is meeting their own procedures and policies, and if their program for executing the requirement is adequate.

NOTE: Inspections of licensed IVD manufacturers are not subject to the preannouncement provisions noted in the QSIT guide and described in IOM 5.2.1.1. However, foreign inspections performed by TB are routinely preannounced to facilitate scheduling. In addition, manufacturers of licensed IVDs are not eligible to participate in the Accredited Persons Program.

C. SYSTEMS DEFINITION

Inspections of licensed IVD manufacturers are to be conducted and reported using the major systems and organization defined in this compliance program. In addition to the areas of inspectional focus described below for each major system, and the Additional Inspectional Information found in Part III., Section E., system assessment should include a walk-through of the facilities whenever possible.

1. Management Controls System

The purpose of the management controls system is to establish quality policy, objectives, and procedures; provide adequate resources for device design, manufacturing, quality assurance, distribution, installation, and servicing activities; assure the quality system is functioning properly; monitor the quality system; and make necessary adjustments. A quality system that has been implemented effectively and is monitored to identify and address problems is more likely to produce devices that function as intended. A primary purpose of the inspection is to determine whether management with executive responsibility ensures that an adequate and effective quality system has been established (defined, documented and implemented) at the firm.

Inspection of the Management Controls System should:

- Evaluate whether an adequate and effective quality system has been established and maintained.
- Verify that a quality policy and objectives have been implemented.
- Review the firm's established organizational structure to confirm that it includes provisions for responsibilities, authorities and necessary resources.
- Confirm that a management representative has been appointed.
- Verify that management reviews, including a review of the suitability and effectiveness of the quality system, are being conducted.
- Verify that quality audits, including re-audits of deficient matters, of the quality system are being conducted.

2. Design Controls System

The purpose of the design control system is to control the design process to assure that devices meet user needs, intended uses, and specified requirements. Attention to design and development planning, identifying design inputs, developing design outputs, verifying that design outputs meet design inputs/requirements, validating the design, controlling design changes, reviewing design results, transferring the design to production, and compiling a design history file help assure that resulting designs will meet user needs, intended uses and requirements.

Inspections of the Design Controls System should:

- Verify that design control procedures that address the requirements of 21 CFR 820.30 have been defined and documented.
- Confirm that design inputs were established.
- Verify that the design outputs that are essential for the proper functioning of the device were identified.
- Confirm that acceptance criteria were established prior to the performance of verification and validation activities.
- Determine if design verification confirmed that design outputs met the design input requirements.
- Confirm that design validation data show that the approved design met the predetermined user needs and intended uses.
- Confirm that the completed design validation did not leave any unresolved discrepancies.
- If the device contains software, confirm that the software was validated.
- Confirm that risk analysis was performed.
- Determine if design validation was accomplished using initial production devices or their equivalents.
- Confirm that changes were controlled including validation or where appropriate verification.
- Determine if design reviews were conducted.
- Determine if the design was correctly transferred.

NOTE: The QSIT guide instructs that during inspections of the Design Control system, a single design project should be selected for review. For inspections of licensed IVDs, investigators have the discretion to evaluate more than one project if they believe additional review is necessary for a comprehensive evaluation of the system.

3. CAPA System

The purpose of the corrective and preventive action system is to collect and analyze information, identify and investigate product and quality problems, and take appropriate and effective corrective and/or preventive action to prevent their recurrence. Verifying or validating corrective and preventive actions, communicating corrective and preventive action activities to responsible individuals, providing relevant information for management review, and documenting these activities are essential in dealing effectively with product and quality problems, preventing their recurrence, and preventing or minimizing device failures.

Note: Installation (21 CFR 820.170) is covered as a QSIT linkage under CAPA.

Inspections of the CAPA System should:

- Verify that CAPA system procedure(s) that address the requirements of the QS regulation have been defined and documented.
- Determine if appropriate internal and external sources of product and quality problems have been identified, and that data from these sources are analyzed to identify existing product and quality problems that may require corrective action. This analysis should include data and information from all acceptance activities, inspection and testing activities, complaints, service, and returned product records.
- Determine if sources of product and quality information that may show unfavorable trends have been identified. Confirm that data from these sources are analyzed to identify potential product and quality problems that may require preventive action.
- Verify that the data received by the CAPA system are complete, accurate and timely.
- Verify that appropriate statistical methods are employed (where necessary) to detect recurring quality problems.
- Determine if failure investigation procedures are followed.
- Determine if failure investigations are conducted to determine root cause (where possible).
- Verify that there is control for preventing distribution of nonconforming product.
- Determine if appropriate actions have been taken for significant product and quality problems identified from data sources.
- Determine if corrective and preventive actions were effective and verified or validated prior to implementation.
- Confirm that corrective and preventive actions do not adversely affect the finished device.
- Verify that corrective and preventive actions for product and quality problems were implemented and documented, and any resultant changes from the firm's approved BLA were reported in accordance with 21 CFR 601.12.
- Determine if information regarding nonconforming product and quality problems and corrective and preventive actions has been properly disseminated, including dissemination for management review.

4. P&PC System

The purpose of the production and process controls system is to manufacture products that meet specifications. Developing processes that are adequate to produce devices that meet specifications, validating (or fully verifying the results of) those processes, and monitoring and controlling the processes are all steps that help assure the result will be devices that meet specifications.

Note: It is important to thoroughly cover Purchasing Controls (21 CFR 820.50), to include outsourced processes, as a QSIT linkage under P&PC whenever P&PC is covered. Additional linkages in the P&PC System include Identification and Traceability (21 CFR 820.60 and 65, respectively), and Handling, Storage, and Distribution (820.140, 150, and 160, respectively).

Inspections of the P&PC System should:

- Verify that the process is controlled and monitored, including in-process and/or finished device acceptance activities as well as environmental and contamination control measures.
- If review reveals that the process is outside the firm's tolerance for operating parameters and/or rejects or that product nonconformances exist:
  - Determine whether non conformances were handled appropriately.
  - Review equipment adjustment, calibration and maintenance.
  - Evaluate the validation study in full to determine whether the process has been adequately validated.
- If the results of the process reviewed cannot be fully verified, confirm that the process was validated by reviewing the validation study.
- If the process is software controlled, confirm that the software was validated.
- Verify that personnel have been appropriately qualified to implement validated processes or appropriately trained to implement processes which yield results that can be fully verified.

NOTE: The QSIT guide instructs that during inspections of the P&PC system, a single manufacturing process should be selected for review. For inspections of licensed IVDs, investigators have the discretion to evaluate more than one manufacturing process if they believe additional review is necessary for a comprehensive evaluation of the system.

D. INSPECTIONAL APPROACHES

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

Level I (Full) Inspection Option

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

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

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

The Level I option includes an in-depth review of the four major systems. The QSIT approach for full inspections recommends the following inspectional sequence: Management Controls, Design Controls, CAPA and P&PC. This inspectional sequence allows the investigator to review design control issues and how the device specifications were established before reviewing the CAPA system. Investigators may, however, start with Management Controls, followed by CAPA, Design Controls, and P&PC. Information from Design Controls and CAPA may be used to select the products and processes for inspecting production and process controls. The systems may be inspected in any appropriate and justifiable sequence in order to perform a timely and effective inspection.

If investigators observe serious deficiencies in one or more systems during the course of a Level I inspection, they may, after consult with their supervisor and an ORA/OE CO, and in the effort to expeditiously pursue appropriate regulatory remedies, revert to the Level II inspection option, provided the minimum two systems are completed (CAPA and either P&PC or Design Controls). The consultation should also include discussion of the necessary documentation to support a possible regulatory action.

Level II (Abbreviated) Inspection Option

The Level II (Abbreviated) option is a focused surveillance inspection that covers two of the major systems, and provides verification of an establishment's continued compliance with CGMP.

The Level II option includes an in-depth review of the CAPA System, and one additional major system, either P&PC or Design Controls, which is to be determined during work planning. Coverage of additional major systems should be rotated in successive Level II inspections, unless otherwise indicated by issues identified during the current or previous inspection. In addition, during the course of a Level II inspection, verification of CAPA activities may require limited coverage of other systems.

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

- The establishment has a satisfactory history of compliance, e.g., at least two successive NAI or VAI inspections
- One of the two previous biennial inspections was a Level I inspection
- The inspection preparation identified no specific trends that may have a significant impact on product safety or quality.

Note: A comprehensive inspection performed under the previous, non-systems based inspection programs can be considered a Level I inspection.

E. ADDITIONAL INSPECTIONAL INFORMATION

1. Cooperative Manufacturing Arrangements:

For further guidance, see:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm069883.htm

a. SHARED MANUFACTURING

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

The manufacturer who prepares the product in its final form will be held responsible for any post-approval obligations, such as reporting biological product deviations and adverse events, unless the manufacturers agree and the approved application states otherwise.

When inspecting shared manufacturing situations, investigators should:

- Determine if the agreements in the applications are being met, particularly as they pertain to the integrity of the product.

b. DIVIDED MANUFACTURING

In a divided manufacturing arrangement, each manufacturer is licensed to manufacture a product in its entirety, but each performs only part of the process. This arrangement is described in supplements submitted to each manufacturer's license. The record requirements for divided manufacturing arrangements are described in 21 CFR 600.12(e). Each manufacturer must have documentation of its responsibility for manufacturing the product.

The manufacturer who makes the product in final form must retain a complete set of manufacturing records for all operations relating to the product, including those operations performed at another facility.

When inspecting divided manufacturing situations, investigators should:

- Thoroughly review the divided manufacturing arrangement and determine if the process as described in the application supplements is being followed. Particular attention should be paid to the conditions under which intermediate product is shipped between the facilities to ensure the integrity of the product.

c. CONTRACT MANUFACTURING

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

however, the manufacturer remains ultimately responsible. The contractor is responsible for complying with CGMP, as applicable.

During the inspection, review a copy of the current contract(s), determine the information listed below, and document in the EIR:

- Extent of services provided;
- Each party's responsibility for the product or operations performed;
- Who prepared the SOPs used by the contractor; and
- Who performed product quality control tests.

If inspecting a contract manufacturer:

- Verify that the license holder is notified of any manufacturing deviations and any manufacturing changes for its licensed product(s).

If inspecting the license holder, who is responsible for final lot release:

- Verify that all records associated with lot release of any given batch are available and have been approved.
- Document how the license holder documents oversight of the contract manufacturer and/or how components are qualified.

2. Establishment Registration

21 CFR Part 807 describes the requirements for establishment registration and product listing for device manufacturers. However, in accordance with 21 CFR 807.20(a), IVD products licensed under Section 351 of the PHS Act do not meet the definition of a device subject to registration and listing under that section. Therefore, licensed IVD manufacturers are not subject to registration and listing requirements under 21 CFR 807 if they only manufacture licensed IVDs.

Instead, establishments that manufacture only licensed IVDs are subject to the registration and listing requirements for manufacturers of human blood and blood products at 21 CFR Part 607, as they are included in the definition of a blood and blood product for that section (21 CFR 607.3(b)).

Licensed IVD manufacturers must submit their initial establishment registration and product listing information within 5 days after either beginning operations or submission of a biologics license application. Establishments must also submit annual registrations between November 15 and December 31, and update their product listing every June and December (21 CFR 607.21).

Investigators can review current registration information for active, inactive and pre-registered establishments by accessing the CBER Blood Establishment Registration database.

During each inspection of a licensed IVD establishment:

- Verify that the establishment registration and product listing information is timely and accurate. All registration and listing observations should be discussed with firm management and reported in the EIR.

3. Change Reporting

For further guidance see:
http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM170166.pdf [1]

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

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

Changes that have a minimal potential to have an adverse effect on the safety or effectiveness of a product may be implemented before being reported to CBER; however, a manufacturer is required to include such changes in its annual reports to the agency.

Data relevant to changes reported in annual reports (e.g., validation data) must be made available during FDA inspections. When a change has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as it may relate to the safety or effectiveness of a product, a manufacturer must submit a license supplement describing the change. If FDA does not advise the manufacturer within 30 days of submission of the supplement that the change requires approval prior to distribution of the product (i.e., a Prior Approval Supplement), the manufacturer may distribute product manufactured using the change pending approval of the supplement. This type of supplement is referred to as CBE-30, or changes being effected in 30 days.

In certain circumstances FDA may determine that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information. Likewise, there may be particular assurances that the proposed change has been appropriately submitted, such as when the change has been validated in accordance with a previously approved protocol. In these circumstances, FDA may determine that the product made using the change may be distributed at the time of receipt of the supplement by FDA. This type of supplement is referred to as a changes being effected, or CBE.

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

If the firm has an FDA-approved comparability protocol (see 21 CFR 601.12(e)) in place for a particular change or set of changes, the firm may be able to report the change in a lower

[1] Please note that the information regarding Blood and Blood Components, Source Plasma, and Source Leukocytes included in this Guidance was superseded in Guidance published in July, 2001. See http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm062891.pdf . The information is correct for other Biological Products.

reporting category if it follows the protocol set forth in the approved comparability protocol supplement when implementing the change.

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

When evaluating reporting of changes to an approved application:

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

Note: Manufacturer's annual reports are submitted based on the specific product approval date, indicated in 21 CFR 601.12(d). Therefore, the annual reports are submitted each year within 60 days of the anniversary date of approval of the application. The Director, CBER may approve a written request for an alternative date to combine annual reports for multiple approved applications into a single annual report submission.

4. Labeling, Packaging, and Shipping

Labeling, packaging, and shipping requirements applicable to licensed IVDs are found in 21 CFR 809.10, 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 809.10, 820.120, and 820.130. Specific wording for labeling is reviewed and approved by CBER.

When reviewing labeling, packaging, and shipping during an inspection:

- 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/OCBQ/DIS/PSB or the product office if there appear to be labeling deficiencies in the firm's products.
- Evaluate whether device packaging and shipping containers are designed and constructed to protect the device from alteration or damage.

5. Lot Release

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

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

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

When reviewing lot release activities:

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

6. Biological Product Deviations (BPDs)

For further guidance see: http://www.fda.gov/cber/biodev/biodev.htm.

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

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

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

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

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

Prior to conducting an inspection, investigators should review the manufacturer's BPD submissions. An assessment of the deviation codes may assist in determining the optional

system to inspect. Otherwise, select a representative sample of reports to verify the adequacy of the firm's corrective actions.

When evaluating BPD information during an inspection

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

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

7. Medical Device Reporting (MDR)

The MDR regulation requires medical device manufacturers, device user facilities and importers to establish a system that ensures the prompt identification, timely investigation, reporting, documentation, and filing of device-related death, serious injury, and malfunction information.

When evaluating an establishment’s compliance with the MDR regulation:

- Verify that the firm has MDR procedures that address the requirements in 21 CFR Part 803.17.
- Verify that the firm has established and maintains MDR event files that comply with 21 CFR Part 803.18.
- Confirm that the appropriate MDR information is being identified, reviewed, reported, documented and filed.
- Confirm that the firm follows their procedures and they are effective in identifying MDR reportable deaths, serious injuries and malfunctions.

8. Corrections and Removals

The Corrections and Removals Regulation (21 CFR 806) requires medical device manufacturers and importers to promptly notify FDA of any correction or removal initiated to reduce a risk to health (the equivalent of a Class I or II recall).

When evaluating an establishment’s compliance with the Corrections and Removals regulation:

- Determine if corrections or removals of a device were initiated by the manufacturer.
- Confirm that the firm's management has implemented the reporting requirements of 21 CFR Part 806.3.
- Verify that the firm has established and continues to maintain a file for all non-reportable corrections and removals per 21 CFR Part 806.20.
- Verify that the firm is complying with the other file-related requirements of 21 CFR Part 806.

F. REPORTING

Note: If, at any time during the inspection, it is determined that a potentially serious health hazard exists, investigators and ORA/OE COs should contact CBER's OCBQ/Division of Case Management (DCM) immediately.

1. Form FDA 483

Record any deviations from 21 CFR Parts 600, 601, 610, 660, 803, 806, 809, and 820, including failure to adhere to license and supplement requirements, on the Form FDA 483. Per the IOM, conditions listed on the Form FDA 483 should be significant, and should relate to an observed or potential problem with the facility, equipment, processes, controls, products, employee practices or records.

Observations relating to Design Controls placed on the Form FDA 483 should be limited to the adequacy of, and adherence to, the procedures and/or controls established by the firm. We do not recommend placing observations on the Form FDA 483 that concern the adequacy, safety, or efficacy of a particular design. Any such concerns should be noted in the EIR and flagged for review by CBER.

"Potential problems" should have a reasonable likelihood of occurring based upon observed conditions, records or events. Do not cite on the Form FDA 483 deviations from draft or proposed regulations or from guidance documents. Present verifiable evidence for conclusions of observed non-compliance with CGMP. Investigators should not use the term "inadequate" without explaining why or how it is inadequate. Refer to policy in the IOM, Chapter 5, Section 5.1.2 and Field Management Directive (FMD) 120 for further guidance on the content of Inspectional Observations.

The most critical observations should be listed first. Similar or repeated observations should be consolidated under a unified observation. Deficiencies that were noted during a previous inspection and remain uncorrected should be included on the Form FDA 483 as repeat deficiencies. Discuss with the manufacturer prior observed deficiencies that have gone uncorrected.

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

2. Systems

Report briefly in the Establishment Inspection Report (EIR) on all systems covered as outlined in Part III, Inspectional, of this compliance 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. These corrective actions may warrant reporting into the FACTS Compliance Achievement Reporting System (CARS), refer to IOM 5.10.2.1.

3. EIR Preparation and Classification

The TB lead investigator will coordinate the preparation of the report. All EIRs are sent to the TB supervisor for review and clearance. For domestic inspections, the investigator and the TB supervisor will endorse and classify the EIR. For foreign inspections CBER, as the home district, will be responsible for final endorsement and classification.

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

The EIR should be endorsed, classified, and submitted in accordance to agency policy and procedures. EIRs should be submitted within established agency time frames. See FMD 86, Establishment Inspection Report Conclusions and Decisions

4. Updating Profile Information in FACTS

Profile information should be entered for all post-market inspections performed under this compliance program. Instructions for updating firm profiles in FACTS are referenced in the IOM Exhibit 5-14. The following additional recommendations are included for licensed IVDs:

- TB investigators should:
  - Enter an initial review status profile of "Further Action Indicated (FI)" as soon as possible after determining that the inspection represents a potential OAI situation.
  - Enter the initial review status profile of NAI and VAI inspections at the completion of the inspection.
- The ORA/OE CO is responsible for ensuring that the final review status profile is entered for all TB domestic inspections.
- CBER is responsible for ensuring that the final review status profile is entered for all TB foreign inspections.

PART IV – ANALYTICAL

NO FIELD ANALYSES ARE PLANNED UNDER THIS PROGRAM.

The routine collection and analysis of physical samples is not planned under this program. If CBER requests sample collection, specific instructions will be provided. Consult with CBER program contacts identified in Part VI B., before collecting samples for agency analysis, except for documentary samples for interstate commerce (collect a documentary sample in accordance with IOM Subchapter 4.4, Documentation and CR, to support regulatory/administrative action).

Contact the CBER Sample Custodian (301-594-6517) before shipping any samples to CBER. No one is routinely available to receive samples over the weekend. Samples evaluated by CBER should generally be shipped to:

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

Collect and ship any samples of a potentially bio-hazardous nature in accordance with IOM Subchapters 1.5 and 4.5.5.8.6.

Original results of analyses will be forwarded to the ORA/OE CO with a copy to the home district and CBER/OCBQ/DCM, HFM-624. Investigators should document in FACTS to whom CBER should send the sample results. If unable to document in FACTS, then use Form FDA 464a, C/R Continuation Sheet.

Copies of collection reports for physical samples must be submitted to CBER/OCBQ/DCM, HFM-624.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

The evaluation of inspectional findings and any resultant recommendation for regulatory action will be conducted in accordance with existing procedures and the Regulatory Procedures Manual (RPM). The TB lead investigator will advise the home district of inspectional and compliance activities related to facilities located within the district.

The decision on the type of action to recommend should be based on the seriousness of the documented deficiencies, and the most effective way to protect the public health. Many licensed IVDs are vitally important in establishing the safety of HCT/Ps and 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 TB.

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

State of Control

A firm is considered to be operating in a state-of-control when it employs conditions and practices that ensure compliance with the intent of Section 501(h) of the Act, and the portions of the CGMP/QS regulations that pertain to their systems. A firm in a state of control produces finished licensed IVDs for which there is an adequate level of assurance of safety, purity, and potency.

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

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

Refer to the RPM to determine the appropriate advisory, administrative or judicial action based on the inspectional findings. Early consultation with CBER/OCBQ/DCM (as well as the ORA/OE CO and the TB supervisor) is critical when immediate action is indicated, e.g., license

suspension, a temporary restraining order (TRO), etc. See RPM Chapter 6 regarding an injunction to protect the public health.

When inspectional findings indicate the potential for fraud, e.g., falsification, counterfeiting, illegal importation, and/or device diversion, the investigator should notify the ORA/OE CO, the TB Supervisor, and OCBQ/DCM (HFM-624), who will alert the appropriate OCI office. The investigator should continue to pursue any public health concerns, in coordination with CBER/OCBQ, concurrently.

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

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

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

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

Prosecution	Fraud, gross, flagrant or intentional violations, health hazards, or serious violations that have not been corrected.
Recalls	If TB believes that prompt removal from commerce of a violative device is necessary, it should proceed in accordance with the requirements of 21 CFR § 810 and established recall procedures found in Chapter 7 of the RPM and 21 CFR Part 7 (Enforcement Policy), Subpart C (Recalls). In the event of serious adverse health consequence or a death, CBER may order a firm to discontinue further distribution and advise customers of the problem, and may subsequently order the recall of a device to the user level in accordance with Section 518(e) of the Act.
Civil Money Penalties	In accordance with Section 303(g)(1)(B)(i) of the FD&C Act, civil money penalties shall not apply to QS violations unless such violation constitutes either a significant or knowing departure from QS requirements, or a risk to public health exists. In addition, Section 303(g)(1)(B)(iii) states that civil penalties shall not apply to Section 501(a)(2)(A) of the FD&C Act when devices have not been shown to be defective.

Deficiencies

The investigator should verify (through actual observation whenever possible) whether or not the firm adheres to the applicable regulations and the law. Inspectional findings that demonstrate a firm is not operating in compliance with regulations and law may be used as evidence for taking appropriate advisory, administrative, or judicial actions.

Significant Deviations

Significant, documented deviations from the law, regulations, or license may warrant advisory, administrative, and/or judicial action. The following, although not all-inclusive, are examples of deviations cited on previously issued licensed IVD advisory, administrative, and judicial actions. Examples are arranged by major system.

Management Controls System

Management with executive responsibility has not established a commitment to quality nor ensured that the quality policy is understood, implemented, has adequate resources, and is maintained at all levels of the organization [21 CFR 820.20(a)]. For example:

- Procedures were not established and maintained for implementing corrective and preventive action, including requirements for identifying the actions needed to correct and prevent the recurrence of nonconforming product and other quality problems [21 CFR 820.100(a)(3)].
- Procedures were not established and maintained to adequately control environmental conditions which could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(c)].
- Complaint files were not maintained [21 CFR 820. 198(a)].
- Complaints were not reviewed, evaluated and investigated involving the possible failure of a device to meet any of its specifications, and in instances where a review, evaluation and investigation was conducted, a record was not maintained of such investigation by the formally designated unit [21 CFR 820.198(c) and (e)].

Adequate organizational structure was not established and maintained to ensure that devices are designed and produced as required [21 CFR 820.20(b)]. For example:

- Quality Assurance does not perform a routine review of product manufacturing and product release records.

Procedures for quality audits were not established and audits were not conducted to assure that the quality system is in compliance with established quality system requirements and to determine the effectiveness of the quality system [21 CFR 820.22]. For example:

- There is no documentation that yearly internal audit reports have been reviewed by management.

Design Controls System

Procedures were not established and maintained for changes to a specification, method, process, or procedure [21 CFR 820.70(b)]. For example:

- Manufacturing process change was not approved by quality unit prior to product distribution, in violation of procedure.

Device master records were not established and maintained that include or refer to device specifications; production process specifications; quality assurance procedures and specifications; packaging and labeling specifications; and installation, maintenance, and servicing procedures and methods [21 CFR 820.181]. For example:

- Device master records for licensed products are not maintained.

CAPA System

Procedures were not established and maintained for implementing corrective and preventive action, including requirements for investigating the cause of nonconforming product and identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems [21 CFR 820.100]. For example:

- Vials failed to meet a release specification, but the vials were released and the failure was not investigated.
- During shipping and packaging operations cracked and broken vials were identified. The cause of the defects was not identified. No investigation or corrective and preventive action was implemented.
- Out-of-specification events occurred due to microbial contamination during bulk and finished product testing. Investigations were not conducted in a timely manner. In many instances, root causes of contamination were not identified, and preventative and corrective actions were not implemented.

Procedures were not established and maintained to ensure that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems [21 CFR 820.100(a)(6)]. For example:

- Procedure allows for repeat testing of OOS results before notifying QA of nonconformities.
- QA was not notified when lots failed to meet the licensed release specification.

Procedures were not established and maintained for receiving, reviewing, and evaluating complaints by a formally designated unit to ensure that complaints are processed in a timely manner [21 CFR 820. 198(a)]. For example:

- Complaints which were manually recorded were often discarded and not entered into the complaint database.
- Complaints, initiated more than three years ago, remained open as of the date of the FDA inspection.

Complaint handling procedures were not established and maintained to ensure that all complaint files are evaluated to determine whether the complaint represents an event which is required to be reported to FDA under part 803 of this chapter, Medical Device Reporting (MDR) [21 CFR 820.198(a)(3)]. For example:

- Procedure which requires MDR assessments was not followed.

MDRs were not submitted to FDA within 30 days of receiving information that reasonably suggests that a marketed device may have malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur [21 CFR 803.50(a)(2)]. For example:

- A complaint for an unexpected result was deemed MDR reportable in August 2010. This report was not submitted to FDA until January 2011.

Biological product deviations (BPD) that may have affected the safety, purity, or potency of any distributed product were not promptly reported [21 CFR 600. 14(a)]. For example:

- BPD reports were not submitted for:
    - During preservative effectiveness testing performed on stability samples of test kit components, the antimicrobial agents in a component was not found to be effective against all bacterial strains from the USP standard panel. Test kit lots containing this component were distributed.
- BPD reports were not submitted in a timely manner. For example:
    - Numerous customer complaints concerning an increased incidence of initial reactive results were received. A BPD report was not submitted to FDA concerning these deviations until more than three years after the complaints were received.

P&PC System

Requirements, including quality requirements, that must be met by suppliers, contractors, and consultants are not established and maintained [21 CFR 820.50(a)]. For example:

- There is no documentation that the supplier of vials was notified when multiple lots of vials failed to meet product specifications.
- Contractors supplying service for maintenance and calibration of water systems, HVAC systems, sterilization, and laboratory equipment have not been qualified.

Production processes have not been developed, conducted, controlled, and monitored to ensure that a device conforms to its specifications [21 CFR 820.70(a)]. For example:

- Container closure integrity testing studies have not been performed for kit reagents.
- There are no data to support the re-use of chromatography columns used for purification.
- During media fill, vials were removed from the total number of vials that were filled and submitted to QC for testing. The removed vials were not incubated and examined for contamination by production or QC.

Process control procedures were not established and maintained that describe any process controls necessary to ensure conformance to specifications, including the approval of processes and process equipment [21 CFR 820.70(a)(4)]. For example:

- Validation report for the use of storage containers does not address follow-up or corrective actions to be implemented for failure to meet defined acceptance criteria.

Procedures were not established and maintained to adequately control environmental conditions that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(c)]. For example:

- Studies have not been completed to support the effectiveness of disinfectants used in the cleaning of manufacturing areas.
- Procedure which requires that daily viable and nonviable particulate air sampling, point-of-fill sampling, and personnel sampling be performed while manufacturing rooms are in use, was not followed
- Environmental monitoring procedure does not clearly define requirements for environmental monitoring and does not prohibit the spraying of hands with alcohol prior to performing personnel sampling.

Requirements were not established and maintained for the health, cleanliness, personal practices, and clothing of personnel in contact with products or environments which could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(d)]. For example:

- Environmental monitoring of personnel is not routinely performed during vial filling operations. Unidentified microbial contaminants have been isolated from the gloves of employees working in these areas.

Procedures were not established and maintained to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(e)]. For example:

- Validation does not support the test sample incubation times specified in the procedure.
- The cleaning processes for Class 100 filling rooms have not been validated.
- Operators in the filling room were noted going back and forth between Class 100 and Class 10,000 areas.

Equipment used in the manufacturing process does not meet specified requirements and is not appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use [21 CFR 820.70(g)]. For example:

- The instrument used for the microbial testing of water has not been qualified.
- The centrifugal air sampler used for the microbial testing of air samples has not been qualified.
- The vialing and labeling machine has not been qualified.

Processes have not been validated with a high degree of assurance and approved according to established procedures [21 CFR 820.75]. For example:

- There is no documentation to demonstrate that the autoclaving of product stoppers multiple times during the wash and depyrogenation process will not affect the stopper's performance.
- Critical processing steps used in the formulation of test kit reagents have not been validated.

Procedures were not established and maintained for monitoring and control of process parameters for validated processes to ensure that specified requirements continue to be met [21 CFR 820.75(b)]. For example:

- Validation study for the recovery of fungal microorganisms has not been shown to be adequate, as consistent recovery of fungal organisms has not been demonstrated.
- Validation of the autoclave and dry heat oven are incomplete, in that a standard load pattern configuration for routine component placement in the units has not been defined.

Adequate acceptance procedures for in-process and finished devices which include inspections, tests, or other verification activities were not established and maintained [21.CFR 820.80]. For example:

- Product lot tested out of specification, however the lot was released to inventory prior to completion of the investigation.
- Product lot was placed on hold after testing positive for microbial growth, however, the hold was removed, and the product was released for distribution prior to completion of the investigation.

Procedures were not established and maintained to control product that does not conform to specified requirements [21 CFR 820.90]. For example:

- Although investigations of failed stability assays had not been completed, lots were approved for release by the QC manager.
- Lots that failed to meet the licensed final release bioburden specification were released.

Procedures were not established and maintained for rework, to include retesting and reevaluation of the nonconforming product after rework in order to ensure that the product meets its current approved specifications [21 CFR 820.90 (b)(2)]. For example:

- Products were reworked, without an approved rework procedure.

Procedures were not established and maintained for the control of storage areas and stock rooms for product to prevent mixups, damage, deterioration, contamination, or other adverse effects of products pending use or distribution [21 CFR 820. 150(a)]. For example:

- Finished products awaiting shipment, in-process products awaiting quality assurance release, quarantined products, and released/unreleased raw materials were co-mingled in the receiving and shipping warehouse
- In-process and released products were co-mingled on shelves in storage areas.

Complete device history records were not maintained [21 CFR 820.184]. For example:

- Device history records do not identify the specific equipment used in the manufacturing processes.
- Device history records do not include product label accountability.

Procedures were not established and maintained to ensure that sampling methods are adequate and that sampling plans are based on valid statistical rationale [21 CFR 820.250(b)]. For example:

- Quality assurance testing of components and finished devices is not based on a documented valid statistical sampling plan.
- There are no data to support the sampling frequency for bioburden testing during filling.

PART VI - REFERENCES AND PROGRAM CONTACTS

A. REFERENCES:

1. Federal Food, Drug, and Cosmetic Act, and Related Laws.
2. Public Health Service Act.
3. Title 21, Code of Federal Regulations, Parts 11, 600, 601, 607, 610, 660, 803, 806, 809 and 820.
4. Compliance Program Guidance Manual, CP 7382.845, Inspection of Medical Device Manufacturers
5. FDA Investigations Operations Manual http://www.fda.gov/ora/inspect_ref/iom/
6. FDA Regulatory Procedures Manual (RPM), Chapter 4- Advisory Actions, Chapter 5 - Administrative Actions, Chapter 6 - Judicial Actions, Chapter 7- Recall and Emergency Procedures, Chapter 9 - Import Operations/Actions. http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm
7. FDA Compliance Policy Guides, Chapter 1- General and Chapter 2 - Biologics. http://www.fda.gov/ora/compliance_ref/cpg/default.htm
8. Glossary of Computerized System and Software Development Terminology, August 1995.
9. Points to consider in the design and implementation of field trials for Blood Grouping Reagents and AHG (Document No. 91N-0467) 1992.
10. Recommended Method for BGR Evaluation (docket No. 845-0181) March 1992.
11. Points to consider in the manufacturing of the in-vitro Monoclonal Antibody Products for Further Manufacturing into BGR and AHG (Document 01N-0466) March 1992.
12. Recommended Method for Evaluating Potency Specificity and Reactivity of AHG (845-0182) 1992.
13. Guidance for Industry, Changes to Approved Applications (Biologics): http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm069883.htm
14. Biological Product Deviations Guidance: http://www.fda.gov/cber/biodev/biodev.htm
15. Global Harmonization Task Force, Quality Management Systems – Process Validation Guidance: http://www.ghtf.org/sg3/sg3-final.html.
16. Guidance on Alternatives to Lot Release for Licensed Biological Products
17. CPG 280.100- Stability Requirements-Licensed In Vitro Diagnostic Products http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073881.htm
18. CPG 280.110-Microbiological Control Requirements-Licensed Anti-Human Globulin & Blood Grouping Reagents http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073882.htm
19. CPG 300.100-Inspection of Manufacturers of Device Components http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073883.htm
20. Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions

21. Assay Migration Studies for In Vitro Diagnostic Devices 1/5/2009 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092751.htm
22. Guidance for Industry: Recommendations for Obtaining a Labeling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) 11/24/2004 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092751.htm
23. Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use, 11/30/2004 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085404.htm
24. General Principles of Software Validation; Final Guidance for Industry and FDA Staff, 1/11/2002 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085281.htm
25. Guidance for Industry: In the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Nucleic Acid Sequences of Human Immunodeficiency Viruses Types 1 and 2, 12/14/1999 http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm077067.htm
26. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological In Vitro Diagnostic Product, 3/8/1999 http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm077093.htm

B. PROGRAM CONTACTS:

CBER

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

1. **Division of Inspections and Surveillance, HFM-650**
   Provides appropriate background material, including license and lot release information, and copies of applicable CBER correspondence and reports, to the Team Biologics investigators prior to scheduled inspections.

   Gilliam B. Conley, Director
   301-827-6220, FAX: 301-827-6748
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- **Program Surveillance Branch, HFM-654**

  Janet Ishimoto, Chief
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- **Biological Product Deviations**

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  Susan.Rogerson@fda.hhs.gov

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

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

   Robert Sausville, Director, 301-827-6201, FAX 301-594-0940
   Robert.Sausville@fda.hhs.gov

   Maria Anderson, Chief, Biological Drug and Device Compliance Branch
   301-827-6201, FAX 301-594-0940
   Maria.Anderson1@fda.hhs.gov

   Mailing Address for CBER Contacts:

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

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

301-594-6517

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

4. **Office of Regulatory Affairs/Office of Regional Operations ORA/ORO**

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

Colleen Hoyt, HFC-130
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5. **Office of Enforcement**

For questions pertaining to recalls:

Recall Operations Staff
Division of Compliance Management and Operations, HFC-210
Office of Enforcement
301-796-8200
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Cecilia Wolyniak
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Cecilia.wolyniak@fda.hhs.gov

For questions regarding compliance policy issues:

Division of Compliance Policy (DCP), HFC-230

Andrea Chamblee, Director
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FAX (301) 827-3670
Andrea.Chamblee@fda.hhs.gov

For questions pertaining to potential regulatory actions:

Division of Compliance Management and Operations, HFC-210
301-796-8200
FAX 301-847-8635

Eugene Leger, Director
(301) 796-8203
Eugene.leger@fda.hhs.gov

PART VII – COORDINATION AND PROGRAM MONITORING

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

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

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

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

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

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

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

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

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

APPENDIX A: LICENSED IVD PRODUCTS – OVERVIEW AND MANUFACTURING METHODS

Technology Overview

Communicable Disease Tests

The testing for communicable diseases includes but is not limited to the blood borne pathogens such as HIV-1 and -2, HTLV-1 and -2, HBV, and HCV**.** Currently licensed donor screening tests include enzyme immunoassay (EIA), nucleic acid tests (NAT), and chemi-luminescent immunoassays (ChLIA). Confirmatory testing methods include neutralization testing, NAT, Western blot, and the immunofluorescence assay (IFA).

General principles behind NAT technology are isolation, amplification, and detection of a target nucleic acid. Typically, the pathogen nucleic acid is isolated from a sample and specific (target) regions of the nucleic acid are exponentially amplified (e.g., polymerase chain reaction or PCR). Detection of the nucleic acid target is achieved by a nucleic acid probe binding to a complimentary nucleic acid sequence derived from the target. Depending on the type of conjugate on the probe, a color change reaction or light emission can result. These events are detected by an instrument which then reports the results. The primers and probes are produced using a variety of molecular biology or biochemical synthesis techniques.

The fundamental principle of licensed immunoassays is a binding event which occurs between antibodies and antigens. Depending on the design of the assay, detection is achieved by capture of the human antibodies, target antigen or both. All of these assays usually employ very specific biologically derived proteins, e.g., 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 active components are purified by typical procedures such as centrifugation, chromatography, or filtration, and when needed 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 some or all 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)
- stop solutions, which are chemical reagents such as sulfuric acid (H2SO4), used to stop the reaction

Immunohematology Tests

Immunohematology reagents include Blood Grouping Reagents, Reagent Red Blood Cells, and Anti-Human Globulin. The term blood group refers to antigens on the surface of the red blood cell membrane that are defined serologically by a corresponding antibody. Red blood cell antigens have detectable characteristics to recognize the presence of a gene. A gene is a segment of deoxyribonucleic acid (DNA) that encodes a particular protein. Each gene occupies a specific location on a chromosome, known as the gene locus. A locus may be occupied by one of several alternative forms of the gene; these alternative forms are called alleles. The terms gene and alleles can be used interchangeably.

In accordance with 21 CFR 312(2)(b)(2)(ii), clinical investigations involving licensed Blood Bank reagents are exempt from the investigational new drug application (IND) requirements outlined in 21 CFR Part 312. The Blood Grouping Reagents defined in 21 CFR Part 660 Subpart C, are used to detect the presence or absence of antigens on donor or patient red blood cells. The source material for Blood Grouping Reagents can be Monoclonal or Polyclonal. The Reagent Red Blood Cells defined in 21 CFR Part 660 Subpart D, are used to detect the presence or absence of blood group antibodies in donor or patient blood. The Anti-Human Globulin defined in 21 CFR Part 660 Subpart F, is used to detect the attachment of antibodies to red blood cell antigens that do not produce visible agglutination.

The ABO system contains four major ABO phenotypes: A, B, O and AB. The four phenotypes are determined by the presence or absence of naturally occurring antibodies, termed isohemagglutinins, directed against missing A and B antigens. The blood bank reagents are used to identify red blood cell antibodies in the serum of transfusion recipients and to test and identify donor blood which lacks the corresponding antigen. The antigens expressed on the red blood cells determine an individual's blood group.

There are three general product types in reference to methodology that can be used in manual tests or with an automated device:

- Traditional Vial reagents
- Column Agglutination products
- Solid Phase products

Manufacturing Methods

Processing of Immunohematology Products

- Polyclonal and Monoclonal

  Polyclonal blood grouping reagents (BGR) are produced by collecting human plasma from donors. In some cases the donors have been immunized to produce the specific desired antibodies. Polyclonal reagents are directed against multiple antigen binding sites found on the original antigen used to stimulate antibody production.

  Monoclonal BGR are made by hybridoma technology, where cells from immunized animals are fused with proliferating myeloma cells. The cells, after screening and

testing, are selected and cultured to produce cell lines that manufacture a specific antibody against a single epitope. In some cases, a mixture of different antibodies against several related epitopes are combined into a single BGR referred to as a monoclonal blend.

- Blood Grouping Reagents

    - Polyclonal BGR

    Pools are created from combinations of individual plasma units (containing the specified antibodies), and are converted to serum by defibrination. Afterwards, adsorption of unwanted antibodies and decalcification is conducted. A preservative is added. The product is optimized for potency, reactivity, and specificity. Adjustment of the physicochemical factors such as pH, protein concentration, and osmolality may be necessary. Formulation occurs according to a standardized recipe, including the antibody, diluent, and/or potentiators.

    - Monoclonal BGR

    A vial of working cell bank is expanded and inoculated in vessels/fermenters that contain culture medium. The antibody is harvested by centrifugation or microfiltration. The antibody is clarified by filtration to remove cells. The filtered supernatant may then be concentrated by ultrafiltration to increase the potency or reactivity to predetermined specifications. After concentration, the antibody is dialyzed with buffer that contains preservatives.

- Anti-Human Globulin

    Anti-human globulin (AHG) can be manufactured from either monoclonal anti-human antibodies or by immunizing a non-human species (e.g., rabbit) with human serum and harvesting the resulting antibodies. The AHG pool is subjected to processing steps such as blending, purification (e.g., adsorption using red blood cells) and standardization of physicochemical factors prior to formulation of the final product. A preservative is added.

- Reagent Red Blood Cells

    Reagent Red Blood Cells (RRBC) are prepared from units of human red blood cells. Some RRBC products are manufactured using units of red blood cells that have been combined (e.g., pooled) together, whereas some products (e.g. panel cells used for antibody identification) require one unit of red blood cells per panel member). All red blood cell units require washing to remove anticoagulants and residual cellular material. The units are washed, centrifuged, and the supernatant discarded. The red cell concentration is determined in order to properly dilute the final product to the required concentration. The diluting medium (e.g., Alsever's solution) is product specific and contains antibiotics to prevent microbial contamination.

- Microbiological Control of Immunohematology Products

  In general, IVDs fall into three categories relative to microbiological control: (1) IVDs labeled as sterile; (2) IVDs that are microbiologically controlled, but are not labeled as sterile; and (3) IVDs that are not microbiologically controlled. Most licensed IVDs fall into the category of microbiologically controlled products, including the immunohematology products BGR, Reagent Red Blood Cells, and AHG. The level of microbiologic control necessary for the manufacture of a specific IVD is established by the manufacturer's design controls (21 CFR 820.30) and process validation studies in accordance with 21 CFR 820.75.

  The requirement for sterility for biological products is found in 21 CFR 610.12; however, this section does not require sterility testing for Reagent Red Blood Cells, Anti-Human Globulin, and Blood Grouping Reagents (21 CFR 610.12(h)(1)). In addition, sterility testing is not currently required for the other licensed IVDs subject to this compliance program (see 21 CFR 610.12(h)(2)).

<u>Ancillary Reagents and Products:</u>

1) Biochemicals

   i) Antibodies

      Extensive qualification testing is usually necessary to ensure that all lots are produced consistently. Antibodies may be designed utilizing a variety of immunological and molecular biology techniques, resulting in monoclonal and/or recombinant products.

   ii) Antigens

      Antigens may be obtained from serum or manufactured using a multitude of biochemical and molecular biology techniques including, recombinant DNA (rDNA) technology, synthesis or derived from cell lines.

   iii) Nucleic Acids

      In Nucleic Acid Tests (NAT), probes, primers, and plasmids may be produced using molecular biology and/or biochemical synthesis techniques.

2) Controls/Calibrators

   Depending on the type of control/calibrator (e.g. negative, positive), these components may be derived from negative or positive human plasma (positive for the pathogen).

3) Preservatives/antibiotics

   All immunohematology reagents are formulated with preservatives and/or antibiotics in order to control any microbiological organisms that may be present.

Methodology:

1) Traditional Vial Reagents

The reagents are filled in vials and testing includes combining the reagent with blood (red blood cells, plasma, or serum) by:

- Manual Tube Method
- Slide Test
- Microplate-manual, semi-automated, or automated

The testing procedures may vary, depending on the target antibody/antigen, and whether it is an IgG or IgM antibody. The testing could include an immediate centrifugation, or incubation, washing, addition of Anti-Human Globulin, and final centrifugation.

2) 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.

For microwell (e.g. 96-well plate) 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. Observe the on-going bead/plate/strip coating and filling operations if possible.

3) Column Agglutination

Blood group antibody is incorporated into the gel; the gel is filled into microtubes of a plastic card or strip of several microtubes of reactants that allows for performance of several tests simultaneously.

4) Conjugation

Adjustments of conjugate concentration 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.

Additional guidance documents for consideration:

1. Points to consider in the design and implementation of field trials for Blood Grouping Reagents and AHG (Document No. 91N-0467) 1992.
2. Points to consider in the manufacturing of the in-vitro Monoclonal Antibody Products for Further Manufacturing into BGR and AHG (Document 01N-0466) March 1992.
3. Recommended Method for Evaluating Potency Specificity and Reactivity of AHG (845-0182) 1992.
4. Recommended Method for BGR Evaluation (docket No. 845-0181) March 1992.

APPENDIX B: PRE-LICENSE AND PRE-APPROVAL INSPECTIONS

BACKGROUND

Section 351 of the Public Health Service Act and section 704 of the Federal Food, Drug and Cosmetic Act provide the regulatory authority to conduct inspections at any establishment where biological products are manufactured. Under 21 CFR 601.20, a biologics license shall not be issued except upon a determination that the product and establishment comply with the applicable regulations.

A pre-license inspection (PLI) or pre-approval inspection (PAI) is performed at establishments named in a biologics license application or supplement to ensure compliance with applicable requirements and to ensure that the data submitted are accurate and complete. A PLI is performed when a biologics license application is submitted for a new product. A PAI is performed when certain, major changes are made and submitted as a Prior Approval Supplement to an approved application.

CBER's policy is to ensure that manufacturing establishments and processes meet the appropriate requirements and comply with the regulations through inspections and review. CBER will determine if a PLI or PAI is necessary based on CBER SOPP 8410 "Determining When Pre-License or Pre-Approval Inspections Are Necessary." The scope of the inspections will be based on the systems approach described in this compliance program in addition to specific areas described in this Attachment.

INSPECTION SCHEDULING AND PREPARATION

A PLI or PAI should be performed when the establishment is in operation, based on inspection team availability, and to meet Medical Device User Fee Act (MDUFA) timeframes. It may be combined with other inspection programs.

The preparation before a PLI or PAI should involve the following:

- Review the CMC section or other sections of the application or supplement for the establishments to be inspected.
- Identify any issue/deviation that needs to be evaluated in more detail while on-site.
- Develop, with the other team members, an inspection plan and strategy specific to the establishment and product being inspected that is consistent with this program's objectives.

INSPECTION TEAM

PLIs and PAIs should be, whenever possible, a team approach with a CBER/OCBQ Division of Manufacturing and Product Quality (DMPQ) inspector as the team lead and a product specialist. CBER requests ORA TB or other participation in CBER PLIs and PAIs. Staff conducting these inspections should be qualified by appropriate training and experience.

CONDUCTING THE INSPECTION

The PLIs and PAIs should be performed using the systems-based approach, covering all systems (if applicable), the equivalent of a Level I inspection. In addition, and as part of the systems-based approach to these types of inspections, the following objectives should also be assessed based on the inspection plan:

- Verify that all relevant data were submitted to the BLA or supplement, and data are accurate and complete.
- Verify that the device history record is accurate and complete when compared to the submission.
- Observe the processes, manufacturing and testing, and compare with the description and/or device history records submitted in the CMC section and other sections of the submission.
- Review process controls, analytical testing, and process validation for the finished device.
- Review facility and process changes not covered in the submission that could affect the product or manufacturing.
- Review design control documentation and compare to data if submitted in the application.
- Review batches or lots that did not meet and met specifications and verify out of specification investigations are completed.
- Review data as needed, determined by submission review for qualification of new manufacturing areas, equipment, and utilities.
- Verify raw materials and components testing have been performed.
- Verify the new product has been incorporated into all aspects of the quality system.
- Review shipping validation for the finished device.
- Verify procedures have been established for reporting of Biological Product Deviation Reports and Medical Device Reports (21 CFR 600.14 and 21 CFR 803, respectively).

INSPECTION REPORTING

Any reportable inspectional observations will be issued to the establishment on a Form FDA 483 consistent with instructions in the IOM. Use the CBER/OCBQ/DMPQ address and phone number as the district office address on the Form FDA 483. The address is: FDA/CBER/OCBQ/DMPQ HFM-670, 1401 Rockville Pike, Rockville, MD 20852-1448, phone 301-827-3031.

The inspection team lead will coordinate with the team concerning the specific establishment inspection report (EIR) sections that each is responsible for writing. The EIR should be written in a very timely manner and in keeping with Medical Device User Fee Amendments (MDUFA) timeframes. All inspectional findings reported on the Form FDA 483 should be resolved in some manner prior to the approval of the application or supplement.