SUBJECT:	IMPLEMENTATION DATE
Inspection of Plasma Derivatives of Human Origin	Upon Receipt
	COMPLETION DATE
	Ongoing

DATA REPORTING	
PRODUCT CODES	PROGRAMS/ASSIGNMENT CODES
57DY[][]	42004

FIELD REPORTING REQUIREMENTS:

A copy of each establishment inspection report (EIR) package in its entirety (including endorsement, classification, exhibits and attachments) is to be submitted to CBER, Office of Compliance and Biologics Quality, Team Biologics Liaison Staff, HFM-604. This includes all violative EIRs for which there is a recommendation for regulatory action. Recommendations will be forwaded expeditiously to the Division of Case Management, HFM-610, for review.

PART I - BACKGROUND

FDA is responsible for, among other things, ensuring that biological products are safe and effective and in compliance with the law and FDA regulations. Biological products are licensed under the provisions of Section 351 of the Public Health Service (PHS) Act (42 U.S.C.) and, because many biological products also fall within the definition of a drug as found in Section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), they are inspected under the provisions of both the PHS Act and the FD&C Act. Biological/drug products are subject to applicable regulations promulgated under both acts, including the Current Good Manufacturing Practice regulations (cGMP) (21 CFR Parts 210 and 211) and the Biologics regulations (21 CFR Parts 600-680). Accordingly, this program is designed to provide uniform guidance for evaluating, through inspections, the conditions under which a particular class of biological/drug products, plasma derivatives of human origin, is manufactured. While similar principles apply, this program is not intended to cover plasma derivatives of animal origin.

Plasma Fractionation

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

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

After fractionation, derivatives undergo further processing to purify and concentrate proteins and to inactivate or remove (clearance) any bacterial or viral contaminants. While early steps in the manufacturing process are not performed aseptically, all final products are sterile. Types of viral clearance include those steps that are part of the fractionation process itself, e.g., pH4/pepsin or polyethylene glycol (PEG) fractionation, or those steps that are deliberately added, e.g.,

solvent/detergent treatment or viral filtration. In some instances more than one viral clearance step is used for a given product. Plasma derivatives are similar to other biological products in that they are protein-based and subject to denaturization at high temperatures. These products are usually filled by using aseptic processing techniques, and cannot be terminally sterilized, although in some instances they can be heat-treated in the final container to effect viral or bacterial inactivation.

A few plasma proteins may also be manufactured by recombinant DNA methods.

Fractionation Products

Each plasma fraction is enriched in specific protein components and is used for a different purpose. In the Cohn-Oncley method, Fraction I contains mostly fibrinogen (not a licensed product), the main protein component of blood clots. Fraction II+III has a high concentration of immunoglobulins (antibodies). Some manufacturers use Fraction IV to prepare licensed products; others consider it a by-product. Fraction IV-1 is the source material for Alpha-1-proteinase Inhibitor (Human); Fraction IV-4+V is the source of Plasma Protein Fraction (Human). Fraction V is the source of Albumin (Human). Most of these products, but not all are intravenously administered. A description of some of the major plasma derivatives follows:

Antihemophilic Factor (Human) (AHF, Factor VIII). AHF protein, one component of the cryoprecipitate fraction of plasma, is used to treat classical hemophilia (hemophilia A). Cryoprecipitate is the solid material that remains after frozen plasma is thawed at a near freezing temperature; it serves as the source of AHF. After the cryoprecipitate dissolves upon warming, the AHF in it can be purified to a high degree, subjected to various viral clearance procedures, and prepared as a lyophilized concentrate. AHF is administered intravenously. NOTE: Even though the clinically active ingredient is the same, AHF is not the same product as Cryoprecipitated AHF, a single donor product prepared in blood banks.

Factor IX Complex (Human) is adsorbed from the plasma fraction remaining after cryoprecipitate removal. It is a heat- or solvent/detergent-treated, lyophilized preparation containing factors II, VII,IX, and X. It is administered intravenously for the prevention and control of bleeding caused by Factor IX deficiency (hemophilia B), and other coagulation disorders.

Coagulation Factor IX (Human) is a highly purified factor IX product that contains negligible amounts of other coagulation factors, and is used to treat hemophilia B.

Immune Globulin (Human) (IG) is a solution of immunoglobulin G (IgG) indicated for prophylaxis of hepatitis A, prevention or modification of measles (Rubeola), and for immunoglobulin deficiency. It is administered intramuscularly.

Additional specific immune globulins for intramuscular administration are obtained from donors whose plasma contains selected high titer antibodies. Products are available for use in the passive prophylaxis of varicella-zoster, tetanus, hepatitis B, rabies, and other infections. Another product, Rho(D) Immune Globulin (Human), is for the prevention of sensitization to the Rho(D) antigen and hemolytic disease of the newborn. Some of the intramuscular immunoglobulin products have been subjected to heat- or solvent/detergent-treatment.

Immune Globulin Intravenous (Human) (IGIV) is a lyophilized preparation that contains intact, unmodified, immunoglobulin. It is often stabilized with monosaccharide (sucrose, glucose, or mannose) and/or Albumin (Human) or glycine. It is indicated for patients with primary immunodeficiency, immune thrombocytopenia and Kawasaki's disease. Additional specific IGIV products are also available and used for such indications as prevention of hemolytic disease of the newborn, or passive prophylaxis of cytomegalovirus or respiratory syncytial virus. All IGIV products have been subjected to viral inactivation/removal procedures by either fortuitous or deliberate methods.

Albumin (Human) (Albumin) is a solution of albumin that is equal or greater than 96% pure. It is heat-treated at 60 degrees C for 10 hours and stabilized with sodium acetyltryptophanate and caprylate. The product may be manufactured in 4, 5, 20, and 25% solutions of protein with 5 and 25% solutions being most common in the U.S. Albumin is administered intravenously, most commonly to compensate for blood loss due to surgery or trauma. Albumin may also be used to treat burn victims to combat blood loss, and to replace plasma proteins in persons with an abnormal decrease in the amount of protein in the blood. It also serves as a stabilizing excipient for other protein products such as clotting factors and vaccines.

Plasma Protein Fraction (Human) (PPF) is 83% or more pure albumin; its use is similar to that of 5% Albumin. Some manufacturers do not produce true PPF but rather label 5% Albumin as PPF, which is acceptable.

Other licensed plasma derivatives include:

Alpha-1-Proteinase Inhibitor (Human)
Antihemophilic Factor (Porcine)
Antihemophilic Factor (Recombinant)

Antihemophilic Factor Concentrate (Recombinant) (For Further Manufacturing Use)
Anti-Inhibitor Coagulant Complex
Antithrombin III (Human)
Coagulation Factor IX (Recombinant)
Digoxin Immune Fab (Ovine)
Lymphocyte Immune Globulin, Anti-Thymocyte Globulin (Equine)
Lys-Plasminogen (For Further Manufacturing Use)
Thrombin (Bovine)

PART II - IMPLEMENTATION

OBJECTIVES

To provide information and guidance to investigators assigned to inspect manufacturers of human plasma derivatives and to prepare investigators to conduct GMP inspections of these manufacturers.

To ensure the safety and effectiveness of plasma derivatives by determining their compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act); the Public Health Service Act (PHS Act); the applicable regulations, including cGMPs (21 CFR Parts 210 and 211) and Biologics regulations (21 CFR Part 600-680); and with standards and commitments made in license applications and/or supplements.

To encourage voluntary compliance by identifying practices which need correction or improvement.

To provide regulatory/administrative guidance to ensure that appropriate enforcement actions are initiated against those manufacturers found to be in significant noncompliance.

PROGRAM MANAGEMENT INSTRUCTIONS

This program is to be followed in the inspection of licensed plasma derivative manufacturers as a part of the regulatory statutory inspection schedule (at least once every two years). These inspections will be conducted by field investigators, with CBER participation whenever possible.

Firms covered under this program include all manufacturers of licensed plasma derivatives of human origin and their products.

Workplanning for these inspections will be coordinated by the Office of Regional Operations (ORO).

Each district is to plan inspectional coverage to ensure that at least a biennial inspection is conducted of each licensed plasma derivative manufacturer in its inventory. Districts are expected to prioritize and schedule more frequent inspections, as appropriate, taking into consideration, among other things, a firm's compliance history.

Each licensed plasma derivative manufacturing facility and its products are to be covered in a single, comprehensive inspection that assesses the adequacy of all significant processes and systems.

Insofar as possible, GMP inspections will be conducted using a team approach with a field investigator leading and a CBER product specialist participating. For those inspections in which CBER product specialists participate, CBER's Team Biologics Liaison Staff (TBLS) will work with the home district to schedule tentative inspection dates. If CBER

participation is not possible, ORA alone will conduct the inspection.

PART III - INSPECTIONAL

OPERATIONS

ORO will make every effort to ensure that each licensed firm is inspected annually or biennially, depending on the firm's inspectional history.

A. INSPECTIONAL PROCEDURES

Review and use applicable sections of Chapter 5 of the Investigations Operations Manual (IOM), and guidance applicable to the manufacture of drug products produced by aseptic processing.

Because of their unique nature as biologics and their regulation and licensing under the PHS Act, there are a number of regulations and standards in addition to 21 CFR 210 and 211 that apply to plasma derivatives. Most are found in 21 CFR Subchapter F - Biologics, most notably Parts 600, 601, 610 and 640; some are found in license and supplement applications. If it is necessary to verify the content of a license application, contact TBLS for guidance.

District offices will coordinate the development of the inspectional strategy with the CBER Team Biologics Liaison Staff (TBLS). Products needing special coverage will be addressed as part of the inspection strategy.

B. INVESTIGATIONS

IN ADDITION TO ROUTINE DRUG CGMP EVALUATION, cover the following:

1. Areas Specific to Plasma Derivatives

a. Source Material

1) Determine the types of source material used and their suppliers. The material must be either licensed Plasma or Source Plasma, or unlicensed Recovered Plasma. Recovered Plasma is a product for which no published standards exist beyond labeling requirements included in 21 CFR 606.121. Licensed manufacturers must provide assurances that plasma for fractionation has been properly processed from the time of collection, and that it does not contain disease-causing agents or contaminants. In particular, there must be evidence that plasma for fractionation has been tested and found negative for Anti-HIV-1, Anti-HIV-2, Anti-HCV (see Part VI, REFERENCES, #23), HBsAg, and HIVag. Individual manufacturers may have additional, self-imposed acceptance criteria, and these must be met in accordance

with SOPs. NOTE: Units positive for Anti-HBc may be accepted as source material.

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

If the source material is not licensed or supplied under a short supply agreement, call (301-594-0653) or FAX (301-594-1944) the CBER Team Biologics Liaison Staff (TBLS) for further guidance.

3) Determine whether incoming source material is inspected and reconciled with shipping documents and test records, and assess the disposition of "hot" (reactive) units. A validated method of tracking each unit of plasma into a plasma pool should be in place.

4) Review source material shipping and storage temperature records. Source Plasma shipping temperature is minus 5 degrees C or lower, and storage is minus 20 degrees C or lower. Source Plasma may on occasion be inadvertently shipped or stored above the prescribed temperatures. See 21 CFR 640.76 for the conditions under which such plasma may be used.

Shipping and storage temperatures for Recovered Plasma must be appropriate for its intended use. These temperatures are usually specified in a short supply agreement.

b. Pooling

At the minimum, it is recommended that pooling be conducted in an environmentally controlled but not necessarily classified area (one with some level of particulate control). Manual pooling may take place either in jacketed tanks or in tanks in a temperature controlled area. Some firms have automatic equipment for "harvesting" plasma from bags or plastic bottles. These units are often equipped with HEPA-filtered areas where plasma is exposed. Although the filters may be designed to meet Class 100 conditions, this environment is not required during the pooling process. All filters should be recertified at an established frequency.

c. Fractionation

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

Manufacturers must show by validation that their procedures yield products meeting prescribed standards. Retrospective validation may be acceptable if processes have been consistent over time, there is past evidence of process controls (in-process and end product data showing lot to lot consistency), and other documentation, as appropriate, showing consideration of effect of change over time.

1) Determine whether there are procedures including preventative maintenance, in place to ensure that no leakage occurs of ethylene glycol if it is used in jacketed tanks and centrifuges. (refer to Part V,#3)

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

d. Column Purification

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

1) Ensure that transfers are made in an environmentally controlled system.

2) Column cleaning, rinsing, testing for residuals, and regeneration procedures are very important. These procedures must be validated and followed. There must be a defined and validated number of uses for each column used, and this limit must be followed. NOTE: Concurrent validation may be performed in accord with the "Guidelines on General Principles of Process Validation."

3) Columns not in use must be stored under conditions that inhibit microbial growth and prevent chemical or physical alteration of the medium. Review the SOPs to ensure that they include the above conditions.

e. Storage of Bulk Fraction

Determine whether bulk concentrates are held and stored in compliance with approved license applications and applicable regulations. See 21 CFR 640.81(d) for Albumin; 21 CFR 640.91(d) for PPF; and 21 CFR 640.102(c) for IG. The specified temperature does not relieve the manufacturer of the responsibility of demonstrating that the conditions used are appropriate for the manufacture of that product. Many manufacturers store bulk paste below -20 degrees C. Bulk concentrates must be stored in clearly identified closed containers.

f. Viral Inactivation/Removal

Viral inactivation/removal is of great importance for the safety of all plasma proteins. Some steps in the fractionation/ manufacturing process itself have been found to inactivate or remove virus; other steps are deliberately taken to inactivate or remove virus. All are important steps and all should be validated. Most validations are performed with one or more marker viruses with properties similar to those of a specific virus in an appropriately scaled-down process. Such small scale validation is acceptable since viruses should not be introduced into a full scale facility.

1) Report on the viral inactivation/removal steps used by the manufacturer.

2) Ensure that SOP(s) are available for deliberate viral inactivation/removal steps for each product manufactured and that all methods have been validated and CBER-approved.

3) Determine whether there is complete segregation of pre-and post-viral inactivation/removal steps (with the exception of products such as Albumin and PPF, which are virally inactivated in final containers). Separate areas with a dedicated air handling unit or single pass air must be used for those steps that occur after viral clearance procedures. Personnel must be either dedicated, or regown after working in other areas. Equipment should be dedicated and should not be mixed with other equipment, e.g., in washing areas, unless adequate cleaning validation and/or clean in place/sterilization in place (CIP/SIP) validated systems are successfully established.

g. Heat Treatment

Heat treatment is one method of clearing infectious agents from biologicals. It is important to ensure that the precise validated conditions of heat treatment are adhered to, because deviations may affect the quality as

well as the safety of the product.

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

Some AHF products are heat-treated in an intermediate process but have to be heated in the presence of added stabilizers which are removed subsequently by ultrafiltration or other means.

Ensure that:

1) Heat treatment of Albumin and PPF begins within 24 hours of completion of final container filling. Heat treatment, i.e., heating for 10-11 hours at 60 degrees C. plus or minus 0.5 degrees, is a necessary viral inactivation/reduction processing step for final containers of Albumin and PPF. See 21 CFR 640.81(e) and 640.91(e).

2) There is an alarm system or other means in place to ensure that the heat-treatment parameters are adequate and that the quality controls are appropriately maintained during the process.

3) Written procedures are in place to describe what to do if the initial heat treatment fails. Is the process "restarted"? Is there a limit to the number of "restarts"? Is there validation to show a lack of adverse impact on the product?

4) Integrity studies and validation of the container/closure system and final containers for Albumin and PPF and other products include the submerged heat treatment steps, and the rinsing of vials after heating. Cages containing a product may be lifted into a heating bath. Check to see if the cages have ever been dropped or banged. Such mishandling may cause hairline cracks in vials.

5) Bath water and post heat-treatment rinse water are monitored for microbial count before each use. Procedures for bath sanitation must be available. See also B.2.b.8.

h. Incubation

Check to ensure that, following heat treatment, final containers of Albumin and PPF are incubated at 20-35

degrees C for at least 14 days. See 21 CFR 640.81(g) and 21 CFR 640.91(g).

i. Examination of Vials

Observe procedures whenever possible.

Ensure that

For Albumin and PPF:

1) Following the incubation period, the final filled vials are examined for turbidity or microbial contamination.

NOTE: Bacterial contamination in 5% Albumin may not be visible by the naked eye until the product becomes heavily contaminated, and contamination in the 20 and 25% products may not be visible at all. Some manufacturers may refer in their SOP to a red color change as indicative of bacterial contamination. Normally, Albumin is straw-colored.

2) Following incubation, contents of turbid final containers are tested for sterility.

3) If growth occurs after incubation, organisms are identified as to genus.

4) No vials showing turbidity or microbial contamination have been issued or used for further reprocessing in the manufacture of other products.

For All Products:

5) Personnel are trained and qualified through the use of established visual controls, examples and/or specific pictures, to detect anomalies in the final product, such as turbidity and/or color change, or cake appearance for lyophilized products.

6) There is 100% inspection for glass and sealing defects. Is there an auditing procedure for accepted units, and alert and action level specifications for false accepts and actual rejects?

7) If automated inspection methods are used, are they validated?

8) Filled vials that are rejected are identified, properly stored and/or destroyed.

9) The firm has appropriate written acceptance and/or

rejection levels for filled vials, whether for contamination or other reasons, and if rejection levels are exceeded, a report of process deviation is completed and issued. **Collect for inclusion in the EIR, information on final inspection quality standards for visual inspections including rejection and acceptance rates for the products being covered.** This data will be evaluated by TBLS to establish industry trends.

10) An action level is set to determine when an entire lot will be rejected.

j. Pyrogens

1) What pyrogen test is the manufacturer using for release testing of final product? If it is other than a rabbit pyrogen test per 21 CFR 610.13, e.g., Limulus Amebocyte Lysate (LAL), ensure that it has been validated (see Part VI, REFERENCES, #14) and approved by CBER.

NOTE: FDA will not permit a manufacturer to retest in rabbits a final-filled product failing a validated and approved LAL test.

2) If the firm has a rabbit colony, ensure that it is maintained and controlled to assure its suitability.

3) If the pyrogen testing is contracted out, determine whether the manufacturer audits the contractor to ensure the appropriateness of such testing.

k. Stability

Each stability program should specify the number of lots and types of lots set aside for study per year. In addition, a stability protocol should be available for each product to specify the criteria needed for storage and temperature conditions. Depending on product specifications, testing criteria generally include appearance, potency, protein content, moisture (lyophilized product), composition, pH, molecular integrity, sterility, and container/closure integrity.

Ensure that the firm has stability programs for final container products and that they include inspection for product contamination. If reprocessing is performed, the stability program must include such lots.

l. Reprocessing/Reworking

Alternative methods of processing are common and are employed mainly to recover clinically useful and

economically valuable material that comes from a moderately limited starting material. CBER allows combinations of fresh source materials, tailings (residual liquid remaining after filling), older powders, frozen pastes, and reworked product to be used to manufacture Albumin or PPF, as long as the final product meets specifications. The potency and molecular integrity of material to be reworked must be evaluated to ensure that it is not compromised. Any reworking/reprocessing procedures must be validated to show that they are equivalent to licensed manufacturing procedures, and must be CBER-approved in a supplement or original license.

It is unacceptable for material from final containers in which bacterial growth occurs to be used for further manufacturing [21 CFR 640.81(g) and 640.91(g)]. Similarly, it is unacceptable to blend lots to reduce the level of adulterants, e.g., endotoxins, below action limits, unless a manufacturing step designed to reduce the adulterants is used, and the process is validated and approved by CBER.

SOPs must be in place that describe the conditions and specifications for reprocessing/reworking, along with SOPs that describe conditions requiring disposal of product. A product that requires reprocessing must be sterile.

Report on any reprocessing/reworking, i.e., repooling, blending, etc. that is performed. Identify the products that undergo such procedures; the conditions under which such procedures are performed; and who approves the reprocessing plan. If failed lots are to be reworked, is an investigation conducted and documented to determine the cause of the failure before reprocessing? See also section B.3.j.4).

m. Lot Release

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

Some manufacturers of well-established biological products have, through approved license supplements, received exemptions from lot release and are on a "Surveillance" program. Manufacturers on surveillance are required to submit samples and/or protocols to CBER

at specified intervals, but they may market their products without receiving lot release. Some plasma derivatives are on surveillance. If a regulatory action is taken against a plasma derivative manufacturer, its product(s) may be removed from surveillance status. See Part VI, REFERENCES, #16.

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

n. Exports

Biological products may be exported in accordance with the recently enacted FDA Export Reform and Enhancement Act of 1996. There are provisions in the PHS Act [section 351(h)] and the FD&C Act [sections 801(d)(3) and (4)] specifically for biological (fractionated) products. Guidance is currently being prepared on this issue. If questions arise regarding imports or exports, contact CBER's Team Biologics Liaison Staff (TBLS); see Part VI, PROGRAM CONTACTS.

o. Reporting of Errors

21 CFR 600.14 requires that CBER be notified promptly of errors or accidents in the manufacture of products that may affect their safety, purity, or potency.

Ensure that any errors or accidents that may have occurred have been reported to CBER. If confirmation of their submission to CBER is needed, contact the TBLS.

p. Reporting of Adverse Experiences

21 CFR 600.80 requires that serious, unexpected adverse experiences associated with the use of a biological product in humans be reported to CBER within 15 days of initial receipt of information or periodically, depending on the seriousness of the adverse reaction. As of January 1, 1997, all manufacturers of blood products, including plasma derivatives, are required to submit monthly reports for adverse experiences involving transmission of infectious diseases.

Review records of adverse events received by the manufacturer and ensure that reports have been submitted to CBER as required. If there are questions or concerns regarding the seriousness of, and therefore the reporting

requirements for, an adverse experience, contact the TBLS. See also Part VI, REFERENCES, #12.

q. Changes to Be Reported

Licensed manufacturers are required to conform to the standards established in their license applications as well as applicable sections of the Biologics regulations. 21 CFR 601.12 requires that manufacturers report to CBER changes in, among other things, production, facilities, equipment, responsible personnel, manufacturing methods and labeling. A document, "Changes to be Reported for Product and Establishment License Applications; Guidance" (see Part VI, REFERENCES, #10), has been issued to provide manufacturers clarification on the types of changes that may or may not be implemented without CBER approval.

> NOTE: The regulations at 601.12 are being revised, as is the Guidance document to which they will refer ("Changes to An Approved Application; Guidance," which will supersede the previously referred to guidance document).

In general, changes which have a minimal effect on the safety or effectiveness of a product may be implemented without being reported to CBER; however, manufacturers will be required to include such changes in annual reports.

Changes with a moderate potential to have an adverse effect on the safety or effectiveness of a product may be implemented 30 days after receipt by FDA of a supplement.

Manufacturers must generate relevant data defining the changes made and make such data available during FDA inspections.

Changes that have a substantial potential to adversely affect the safety or effectiveness of a product must await approval of a supplement prior to distribution of the product.

1) Request a list of significant changes/modifications made to products, processes, quality control, equipment, facilities, systems, and/or responsible personnel since the last inspection, and include it as an exhibit in the report.

2) Review any changes which the manufacturer has determined do not require a supplement and that have not yet been included in an annual report to CBER, and describe them in the inspection report. Determine if

changes have been validated, when appropriate. If there is any question as to whether or not a change should have been reported, or whether a change is considered to be minimal, moderate, or substantial, contact the TBLS.

2. Systems

a. Environmental Control Systems

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

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

Generally, less frequent monitoring is expected in areas in which upstream steps are performed, e.g., pooling and fractionation. These steps may be performed in unclassified, but "controlled" environments (ones with some level of particulate controls). As the process moves further downstream, e.g., purification, more frequent monitoring is expected. Purification areas should be classified to a minimum of Class 100,000. With the exception of plasma pooling and fractionation, which are known to generate non-viable and viable particulates, monitoring should be performed during production. Environmental monitoring of particle counts in areas in which there are alcohol vapors may have to be performed with explosion-proof equipment.

1) Determine whether the above procedures are in place and followed.

2) Evaluate the firm's aseptic processing areas (filling and lyophilization) using 21 CFR 211.42(c)(10) and the "Guideline on Sterile Drug Products Produced by Aseptic Processing" (see Part VI, #15) as guides.

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

4) Ensure that if limits are exceeded, an investigation is conducted and appropriate action is taken. What is done with products produced under out-of-limit conditions?

5) Microbial identification, especially in aseptic areas, should be performed. Check to see if trend analysis is done.

b. Water Systems

1) Review water system diagrams and inspect the system to determine that the diagrams adequately reflect the current as-built conditions. While inspecting the system, look for dead legs and evidence of leaks. All valves and connections should be of sanitary design.

Source water used to feed the water treatment system should meet EPA or comparable potable drinking water standards as directed in the USP. If the source water is from a municipal source, records of EPA tests provided by the municipality may be accepted; however, periodic testing of identified parameters should be conducted to ensure that the water meets standards as it enters the firm.

2) Determine the source of water and how and with what frequency incoming water is sampled and tested. All water treatment components, e.g., sand filters, carbon filters, deionizing units, and reverse osmosis units, should be maintained according to manufacturer's specifications, and periodically monitored to ensure proper performance.

3) Are SOPs for maintenance, replacement, regeneration and/or sanitization of water treatment components in place and followed? Are all instruments, gauges, meters, etc., routinely calibrated?

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

WFI may be generated by distillation or reverse osmosis. A few foreign firms have been approved for ultrafiltration. WFI should meet USP chemical and endotoxin specifications. Additionally, the action limit for WFI is expected to be 10 CFU/100 ml.

All accessible use points should be monitored weekly, in a rotating fashion, so that some point on each distribution system is sampled daily. Other points in the system should also be monitored, e.g., entry to and exit from storage tanks.

WFI systems are generally of a continuous flow design. If not, procedures should be in place for "batching" and discarding the water.

4) Review firm's procedures and controls for the production, monitoring, and testing of all types of water used. Does water quality meet appropriate specifications? Are alert levels based on historical data? Is there monitoring of data that are generated? Is trend analysis done? Do procedures include appropriate actions to take when alert and action levels are exceeded?

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Because fractionation is a cold process, cold WFI systems, rather than point of use heat exchangers, are common in plasma fractionation facilities. Ambient systems may also be encountered. If heat exchangers are used they should be of sanitary design. Procedures should be in place and followed for monitoring temperature and taking action when temperature is not maintained. It is especially important that sanitization procedures be in place and followed to maintain microbiological control in systems run at less than 65 degrees C, and that the procedures are validated with respect to frequency and duration. Any change in parameters should be validated and approved by QC/QA. Procedures for periodic sterilization of water distribution systems should be validated and followed.

5) Have the sanitization and sterilization procedures been validated? Are these validated procedures followed?

6) Review the manufacturer's monitoring and maintenance of cold and/or ambient loops.

7) Ensure that all water storage tanks are equipped with hydrophobic vent filters to prevent microbial contamination. Evaluate replacement procedures. Do they include integrity testing of filters after use?

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Water used to heat-treat and to rinse product containers after heat-treatment must be suitable for its intended use and should not adversely affect the products.

Water used for heat-treatment of products should have an

established microbial limit, and should be monitored to ensure that the requirement is met. Bacteriostatic or bacteriocidal agents, e.g., chlorine and ozone, may be added to this water to ensure limits are not exceeded.

Water used to rinse product containers after heat treatment should also be controlled for microbiological contamination. . Potable water is not acceptable; ideally, WFI should be used.

8) Review the manufacturer's procedures and specifications to ensure the quality of heat treatment water and post-heat-treatment rinse water. Evaluate whether the firm's handling of heat treatment and post-heat treatment rinse water may be a potential source of microbiological contamination of products.

See Part VI, REFERENCES, #20.

c. Heating, Ventilating and Air Conditioning Systems (HVAC)

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

Procedures should also be in place for monitoring other parameters such as temperature and humidity. Fractionation areas or "halls" are generally kept cold. As a result, condensate often forms on pipes and tanks. This may result in rusting of equipment surfaces and puddles on floors if maintenance procedures are not in place. Humidity controls should be in place in upstream processing and aseptic processing areas, and humidity should be monitored in aseptic processing areas.

1) Review procedures for controlling and monitoring pressure differentials, humidity, and temperature. Do procedures include actions to be taken when results are not within established limits? Is the impact of out of limit results on the product adequately addressed?

* * *

All high efficiency particulate air (HEPA) filters should be recertified at least annually. Recertification should include integrity testing of the HEPA filters with an appropriate challenge aerosol, e.g., diocytl phthalate (DOP) or an alternative aerosol that has been determined to have similar or acceptable physical characteristics,

for detection of leaks; air velocity studies; particle counts; and in aseptic areas, laminarity (e.g. smoke studies).

2) Refer to section B.2.a., "Environmental Control Systems," for guidance on monitoring and evaluation of air quality, filtration, air flow, particulate concentration and microbial counts.

d. Steam Generation and Distribution Systems

1) Determine whether clean, or pure, steam systems are monitored periodically to ensure that the condensate meets WFI specifications. No additives should be used in clean steam generators.

2) Evaluate procedures and test results.

e. Clean in Place and Sterilization in Place (CIP/SIP) Systems

CIP systems are often used in fractionation facilities. There should be proper control of cycles and periodic evaluation of cleaning efficacy (e.g., testing of rinse water for upstream processing equipment). SIP may also be used in downstream processing areas for sterilization of equipment. As with CIP, there should be proper control of cycles and periodic evaluation of the adequacy of the sterilization.

1) Cover the CIP/SIP systems used by the firm. Determine which equipment, containers/closures, etc. are cleaned and/or sterilized by which process.

2) Evaluate the firm's validation procedures for all CIP/SIP processes. See Part VI, REFERENCES, #19.

f. Depyrogenation and Sterilization Processes

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

2) Determine if periodic revalidation of the depyrogenation and sterilization equipment is performed. Evaluate the adequacy of the equipment validation.

g. Aseptic Filling

1) Observe the aseptic filling process directly, when

possible, and evaluate aseptic technique. See also Environmental Control Systems (section B.2.a.).

2) Are sterilizing filters validated for product compatibility and microbial retention? Many plasma derivatives share product attributes such as viscosity and pH, therefore, studies may be combined. Evaluate validation of sterilization of filters. Ensure that integrity testing is performed on filters post-fill and that bubble points are in keeping with manufacturer's and validated specifications.

3) Review the program in place for qualification of filling operators. This should include monitoring of gowning technique to ensure compliance. Are written procedures for gowning in place and followed? Is periodic sanitization of gloved hands, using validated sanitizing agents, performed?

4) Evaluate the firm's media fill procedures and test results. Ensure that all operators and shifts are covered. Do media fills encompass all events occurring during normal operations, including duration of fills? Do they represent all volumes filled? This may be done by bracketing of large and small size containers, particularly when vial openings are similar for many sizes represented. Are worst case assessments, including any manual manipulations or maintenance functions included? If product(s) is lyophilized, is this process "mimicked" during media fills? (NOTE: Lyophilization cycles should not be performed on media-filled vials.) What are the alert and action levels set, and what action is taken when these levels are reached or exceeded? If excursions occurred, were investigations conducted and appropriate corrective action taken? After the initial validation, are media fills conducted at least twice per year?

5) Some bulk products are held after sterile filtration prior to filling. Determine whether the holding period has been validated.

6) Evaluate all connections and transfers to ensure that they are made in an aseptic manner.

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

8) If the duration of filling is lengthy, have time

limits been set and validated to ensure that the duration of the fill does not affect the potency of the product and susceptibility to microbial contamination?

9) Check placement of viable and non-viable monitoring equipment and how often monitoring occurs.

10) Is an SOP in place for interruption of the fill, should it occur?

See Part VI, REFERENCES, #15.

h. Lyophilization

1) Review and observe, when possible, transfer of product to the lyophilizer. This transfer should be done under Class 100 conditions, or as otherwise approved by CBER.

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

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

See Part VI, REFERENCES, #21.

i. Equipment Calibration

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

Is all testing, measuring, and monitoring equipment calibrated, periodically checked for accuracy, and recalibrated? How frequently, and what is the source of the standards used?

j. Computer Systems

1) Review all computer systems in use at the firm and the way they affect manufacturing processes.

2) Ensure that:

a) Software affecting manufacturing processes is validated by using approved methods;

b) There are clear procedures to control software changes; and

c) There is thorough documentation of testing procedures.

See Part VI, REFERENCES, #17.

3. General

a. Quality Assurance/Quality Control

1) Review and evaluate the firm's quality assurance and quality control procedures and programs. A good QC system should include validation of all procedures and equipment; and should be able to identify factors critical to making quality products, detect and control out-of-specification products, and control any changes in the manufacturing process.

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

b. Personnel

1) Determine if there is a training program for all employees that includes applicable FDA law and regulations, assigned duties, company SOPs and policy. Is training documented? Do personnel have a basic understanding of the principles and concepts that relate to their assigned duties? Are personnel able to competently perform their jobs using the relevant SOPs?

2) Are qualified persons responsible for training employees?

c. Buildings and Facilities

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

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

3) Examine the procedures and areas for segregating and storing raw materials; quarantined, rejected, in-process, and released products; and for the movement of product

from pre-viral inactivation to post-viral inactivation areas to prevent cross-contamination.

d. Equipment

1) Ensure that key equipment and procedures (those that could affect product quality, e.g., autoclaves, heat treatment baths, filling equipment and product contact surfaces, filling and closing of containers, lyophilizers, depyrogenation equipment) used by the firm are suitable for their intended uses.

2) Is key equipment appropriately cleaned or tagged as to status, identified, calibrated, inspected or checked, qualified and/or validated, and revalidated when necessary, according to a written program? (Refer to "Guideline on General Principles of Process Validation"; see Part VI, REFERENCES, #11).

3) Are maintenance programs/procedures in place and followed?

4) Review SOPs for equipment cleaning procedures and determine if they are validated and followed. Equipment, e.g., tanks for plasma pooling and fractionation must be cleaned, but not necessarily sterilized. See Part VI, REFERENCES, #19.

e. Containers and Closures

1) Does the firm have adequate written procedures describing the receipt, handling, sampling and storage of containers and closures, especially those that need to be sterile and/or pyrogen-free?

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

3) Review the procedures and controls used by the firm to verify and ensure suitability of containers and closures. Evaluate procedures used by the firm to validate the container/closure systems used. See also section B.1.g.4. Report any changes in container/closure systems that have not been validated.

4) How are containers handled after receipt and prior to filling to prevent damage and contamination? Because the final containers are glass vials, cracks and breakage can be a problem. Cracked vials may be difficult or impossible to see by an untrained eye.

5) Review SOPs for reconciliation of final containers.

f. In-Process Controls

1) Evaluate the specifications and procedures for testing in-process materials to assess strength, quality and purity as appropriate, e.g., potency, and protein composition.

2) Evaluate bioburden data on non-sterile bulk. Are limits in place? Is trending performed? How are samples handled?

g. Labeling Controls

Review procedures in place for the examination, control, and use of labeling materials.

See Part VI, REFERENCES, #22 and 24, for specific labeling statements.

h. Holding and Distribution

1) Are warehousing and shipping procedures designed to prevent damaging of products? Are procedures in place for handling damaged vials or other breakable material, e.g., syringes, if an accident occurs?

2) Are warehouse temperatures compatible with labeled product storage temperatures?

3) Does the firm have an adequate SOP for conducting recalls? Have there been any recalls?

4) Determine whether the firm maintains at its corporate offices a current list of authorized distributors, as required by section 503(e)(1) of the FD&C Act.

5) Are quarantined areas for recalled, returned, and unreleased products controlled?

i. Laboratory Controls

1) Review and evaluate the firm's methods for sampling and testing of products for sterility, potency, pyrogens, and conformance with final specifications. Have test methods been appropriately validated for all products on which they are used? Review raw testing data and compare to those reported into the batch production records.

See Part VI, REFERENCES, #13.

2) Review the SOPs for investigating product test failures. Are they adequate, followed?

3) Are sample storage temperatures monitored? Are procedures in place to prevent mix-ups where product samples are stored?

4) Are reference standards for testing in date and on a suitable schedule for determining continuous suitability for use?

5) How are products transported to the QC laboratory?

6) Are proper conditions maintained to insure product integrity?

j. Records and Reports

1) Review batch production and control records of representative lots manufactured since the last inspection for completeness and for review and approval by the quality control unit before release of each lot. Manufacturer's production and disposition summaries are helpful in identifying problematic batch production records for review. Are any downtimes in the filling procedure recorded?

Final product specifications for Albumin, PPF and IGIV should include Prekallikrein Activator (PKA) limits. NOTE: PKA has been held responsible for hypotensive reactions in some recipients. Hypotension is a condition which the administration of Albumin and PPF is intended to overcome.

2) Review laboratory records for the results of tests and their comparison with established standards.

3) Request a list of all failed final and in-process lots, including lots that failed the initial sterility test, and a list of all deviations. Determine the disposition of any lots that have failed or been withdrawn since the last inspection.

4) Review records of investigations of unexplained discrepancies or failures for compliance with 21 CFR 211.192. Are unexplained discrepancies, or failures of batches or components to meet specifications, thoroughly investigated and documented, and is the investigation extended to other batches with which they may have been associated?

5) Examine records of major manufacturing equipment

calibration, checks, inspection, maintenance, cleaning, sanitizing, and use; and laboratory equipment calibration. See section B.3.d.2.

6) Review complaint files (21 CFR 211.198); reports of errors and accidents (EARs) in the manufacture of products that may affect their safety, purity or potency (21 CFR 600.14); and reports of adverse experiences associated with the use of a biological product in humans (AERs) (21 CFR 600.80). Were incidents properly investigated, documented, and reported as required? If another location handles EARs or AERs, include in the report the name and address of the location and the name of the person(s) responsible for handling them. Collect copies of any SOPs that describe how the location being inspected interacts with the office responsible for handling these reports.

7) Obtain a list of lots withdrawn because of the potential of Creutzfeldt-Jacob disease contamination. What is the disposition of these lots?

C. SAMPLE COLLECTION

1. Sample collection may be requested by CBER, in which case specific instructions will be provided. If official samples are not requested, but the inspection team believes that their collection is warranted, contact Product Release Branch, Division of Manufacturing and Product Quality, (301 594-6517), for guidance prior to collecting them.

Contact the CBER Sample Custodian (301 594-6517) before shipping any samples. Ship to:

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

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

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

D. INSPECTION TEAM

Insofar as possible, inspections will be conducted by a team consisting of a district investigator and CBER product specialist(s).

E. REPORTING

1. Notify supervisor or District equivalent immediately if a potentially serious health hazard exists. That person in turn should immediately contact CBER Division of Case Management, 301-827-6201.

2. Report on all major areas or systems investigated as outlined in PART III, Investigations, regardless of findings, for the first inspection of each manufacturer covered under this program (unless the prior inspection report included all necessary information), and subsequently for firms inspected and found to be out of compliance. Utilize Subchapter 590 of the IOM for guidance in reporting inspectional findings.

3. Obtain copies of specifications and/or SOPs that are regarded as inadequate and explain why this conclusion was reached. Actual operations as described in SOPs should be observed.

4. The field, as lead, will coordinate the preparation of the report. The report will be endorsed, classified, and submitted in accordance with agency policy and procedures. Violative reports will be submitted within agency established time frames.

5. Send a copy of each establishment report package in its entirety, including endorsement and classification, to CBER's Team Biologics Liaison Staff (see Part VI, Program Contacts).

6. See Part V for a list of violative conditions which may warrant regulatory action.

PART IV - ANALYTICAL

No field analyses are projected under this program.

Because of the lot release program for licensed biologics [described in Part III,B.1.m)], CBER receives samples and test results for plasma derivatives on a routine or quarterly basis. A program for post-release sampling is also in the planning stage. Therefore, routine sample collection is unnecessary.

Any samples that may be collected during an inspection (either CBER-requested or for cause) will be analyzed by CBER laboratories, e.g., Division of Product Quality Control, HFM- 230, or Division of Hematology, HFM-330. See instructions for shipping in Part III,C,1.

Results of analyses will be forwarded to the appropriate district.

Copies of collection reports for physical samples must be submitted to Division of Case Management, HFM-630, Office of Compliance, CBER.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

Promptly evaluate violative conditions during and following an inspection in order to ensure product safety. In cases in which an expeditious regulatory or administrative action recommendation (i.e., seizure, injunction, prosecution, or license suspension) appears appropriate, contact CBER's Division of Case Management, HFM-610, immediately.

Consider the therapeutic significance and relative availability of the product(s) as well as the potential adverse effect of cGMP deviations on the finished product(s) in determining appropriate regulatory and/or administrative action.

If voluntary action is not appropriate or accomplished, or the deviations pose a threat to the consumer, formal regulatory and/or administrative action should be recommended. The decision on the type of action to recommend should be based on the seriousness of the problem and the most effective way to protect the consumer. Documented deviations representative of regulatory significance may warrant regulatory and/or administrative actions. Refer to the Regulatory Procedures Manual, Chapter 4, Subchapter on Warning Letters; Chapter 5, Subchapter on License Revocation or Suspension; and Chapter 6, Subchapters on Seizure, Injunctions, and Prosecution (Part VI, REFERENCES, #6).

Send recommendations for regulatory actions along with copies of EIRs, including exhibits and attachments, as well as endorsement coversheets, to CBER, Office of Compliance and Biologics Quality, Team Biologics Liaison Staff (TBLS), HFM-604. (See Part VI, PROGRAM CONTACTS.) The TBLS will forward recommendations to the Division of Case Management, HFM-610. (NOTE: Currently there is no direct reference authority for Warning Letters to plasma derivative manufacturers.)

As a general rule, because all plasma derivatives must be sterile and aseptically filled, deviations in the areas of sterile filtration, filling, environmental monitoring, and water quality are considered significant. Additionally, deviations specific to biologics which are considered significant include failure to report errors and accidents, or incomplete and/or untimely reporting of serious or unexpected adverse experiences associated with the use of biological products.

The following is a list of deviations which have been included in previous regulatory actions taken by CBER. It is not all inclusive and is not intended to limit the investigational process to these specific issues. The list is organized into the areas consistent with 21 CFR Part 211, cGMPs for Finished Pharmaceuticals, and also includes relevant sections of 21 CFR, Parts 600-680. See 21 CFR 211.1(b) regarding the scope of the 211s as they apply to biological products. The list may not include specific deviations of 21 CFR Part 211 which have been previously supported by CDER in its regulatory actions involving pharmaceutical products; however, such deviations are not precluded from

consideration for regulatory action if observed in inspections of plasma derivative manufacturers. This list provides guidance in determining the classification and endorsement of the EIR:

1. Organization and Personnel (21 CFR 211.22-34; 600.10)

   a. Inadequate training in cGMPs, e.g., not continual or adequate, incomplete, and/or not given before implementing new or revised procedures.

   b. Unauthorized personnel in limited access areas.

   c. QC unit lacking adequate responsibility and authority and/or QA/QC oversight lacking.

2. Buildings and Facilities (21 CFR 211.42-58; 600.11)

   a. Adequacy of cleaning and sanitation methods not ensured as evidenced by:
   . chipped paint
   . rust
   . water dripping from pipes and ceiling, and/or
   . cleaning procedure effectiveness not established.

   b. Environmental monitoring procedures not adequate and/or established, e.g.:
   . microbial and particle counts not conducted during sterile filtration
   . viable particulate monitoring not performed during filling operations or in other classified areas
   . inadequate investigation conducted when action limits are exceeded, and/or
   . significant lapses in sterile media fill procedures

   c. Manufacturing control systems inadequate to prevent contamination or mixups, e.g., inadequate separation of:
   . pre-viral inactivated products from post-viral inactivated products
   . released, quarantined, and rejected products, and/or
   . bulk and other in-process materials

3. Equipment (21 CFR 211.63-72; 600.11)

   Inadequate validation, calibration, maintenance, and/or cleaning.

4. Control of Components, Product Containers and Closures (21 CFR 211.80-94; 600.11(h), 601.22, 610.15, 640.80(b), 640.90(b), 640.100(b)

   a. Area for component sampling inadequate to prevent contamination of

controls or other components.

b. Flow of materials between areas or buildings not specified.

5. Production and Process Controls (21 CFR 211.100-115; 600.11(g)

a. Written procedures designed to prevent microbial contamination, including validation of water and HVAC systems and aseptic processing, not established and/or followed.

b. Validation studies of heat-treatment and purification steps, aseptic filling, and/or changes in manufacturing processes inadequate and/or lacking.

c. Appropriate time limits for completion of each phase of production not established.

d. Written procedures for the execution of production and process control functions not established, incomplete, and/or not followed.

6. Packaging and Labeling Controls (21 CFR 211.122-137)

a. Access to labels not controlled.

b. Lack of written procedures describing in detail the handling of labeling and packaging materials.

7. Holding and Distribution (21 CFR 211.142-150)

a. Products not stored under proper temperature conditions.

b. Lack of written procedures for distribution of products.

8. Laboratory Controls (21 CFR 211.160-176; 610.1-15)

a. Maximum load configurations for lyophilization not established or validated.

b. Products distributed prior to release by QC unit.

9. Records and Reports (21 CFR 211.180-198; 600.12)

a. Records, e.g., batch, QC, equipment, incomplete.

b. No record of investigation of unexplained discrepancies or batch failures.

c. Failure investigation record lacked extension of investigation to

other possibly associated batches.

d. Complaint handling procedures not maintained.

10. Licensing (21 CFR 601.10-22)

a. Important changes not reported to CBER.

b. Product not manufactured as described in license application.

PART VI - REFERENCES AND PROGRAM CONTACTS

REFERENCES

1. Federal Food, Drug, and Cosmetic Act, as Amended.

2. Public Health Service Act, Biological Products, Sections 351 and 352 (#D0018)*.

3. Title 21, Code of Federal Regulations, Parts 210, 211, 600, 601, 610, and 640.

4. Standard Operating Procedure (SOP), CBER/ORA Joint Inspection Program.

5. Investigations Operations Manual (IOM).

6. Regulatory Procedures Manual (RPM), Chapter 4, Advisory Actions; Chapter 5, Administrative Actions; Chapter 6, Judicial Actions; and Chapter 10, Other Procedures, EIR Conclusions and Decisions.

7. Compliance Policy Guides, e.g., applicable sections of Sub Chapter 130; sections 110.100, 205.100, 210.100, 230.100, and 480.100; and Sub Chapter 480.100.

8. Compliance Program Guidance Manual, Program 7356.002, Drug Process Inspections; and Program 7356.002A, Small Volume Parenterals.

9. Federal Register/May 3, 1996/Proposed Rule, Current Good Manufacturing Practice; Proposed Amendment of Certain Requirements for Finished Pharmaceuticals (#D0293),* (#0293)**.

10. Changes to be Reported for Product and Establishment License Applications; Guidance (#0214)**. (Will be superseded by "Changes to an Approved Application; Guidance," Notice of Availability of which will be published in the Federal Register)

11. Guideline on General Principles of Process Validation (#D0063)*.

12. Guideline for Adverse Experience Reporting for Licensed Biological Products (#D0150)*,(#0150)**.

13. Guideline for Determination of Residual Moisture in Dried Biological Products (#D0098)*.

14. Guideline On Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices (#D0066)*.

15. Guideline On Sterile Drug Products Produced by Aseptic Processing (#D0064)*, ***.

16. Guidance on Alternatives to Lot Release for Licensed Biological

Products (#D0182)*.

17. Guide to Inspection of Computerized Systems in Drug Processing***.

18. "Biotechnology Inspection Guide," November 1991, ORO/ORA.

19. "Guide to Inspections of Validation of Cleaning Processes," July 1993, ORO/ORA.

20. "Guide to Inspections of High Purity Water Systems," July 1993, ORO/ORA.

21. "Guide to Inspections of Lyophilization of Parenterals," July 1993, ORO/ORA.

22. Letter to All Plasma Derivative Manufacturers and to ABRA; Warning Statement for Plasma Derivative Product Labeling, October 7, 1996 (#D0329)*, (#0329)**.

23. Letter to All Manufacturers: Implementation of testing for Hepatitis C virus RNA by polymerase chain reaction (PCR) of intramuscular immune globulin preparations, June 13, 1996 (#D0306)*, (#0306)**.

24. Letter requesting all manufacturers immediately to revise warning section for package insert on Thrombin, January 24, 1996 (#D0271)*.

* A hard copy may be obtained from CBER's Office of Communication Training and Manufacturers Assistance, HFM-40, by calling 301-827-1800 or 1-800-835-4709, and using the ID# beginning with a "D" following the document name.

** A FAX copy may be obtained by calling 301-827-3844 or 1-888-CBER-FAX (1-888-223-7329) and using the ID# without a "D" following the document name.

*** A hard copy may be obtained from Division of Communications Management, HFD-210, FDA/CDER, 5600 Fishers Lane, Rockville, MD 20857.

PROGRAM CONTACTS

CBER

Questions regarding CBER policy or requests for guidance:

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

301 827-6191

Potential Regulatory Actions:

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

ORA

Questions regarding ORA policy or requests for guidance:

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

PART VII - CENTER RESPONSIBILITIES

Licensing

The Team Biologics Liaison Staff (TBLS), Office of Compliance and Biologics Quality (OCBQ), CBER, will be responsible for ensuring that appropriate licensing and supplement information and copies of applicable correspondence and reports are provided in inspection profiles to district offices in which the affected manufacturers are located.

Program Review and Evaluation

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

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