COMPLIANCE PROGRAM GUIDANCE MANUAL

Imported CBER-Regulated Products

7342.007

[See 7342.007 Addendum for Imported Human Cells, Tissues, and Cellular and Tissue-based Products]

Implementation Date: April 1, 2008

Completion Date: September 30, 2011

Product Codes:

57A	Antitoxins (e.g., Botulism Antitoxin)/Antivenins (e.g., snake, spider)
57B	Immunization Toxoids (e.g., Diphtheria Toxoid, Tetanus Toxoid)
57C	Viral Vaccines (e.g., Rabies, Yellow Fever, Small Pox, Influenza Vaccines)
57D	Blood & Derivatives (e.g., Whole Blood, Red Blood Cells, Albumin, Immune Globulin)
57E	In-Vivo Diagnostic Products (e.g., Tuberculin PPD (skin test))
57F	In-Vitro Diagnostic Products (e.g., Hepatitis B Surface Antigen and Human Immunodeficiency Virus test kits, Reagent Red Blood Cells, Blood Grouping Reagents)
57G	Allergenic Products (e.g., Allergenic Extracts, animal allergens, venoms)
57H	Bacterial Vaccines/Antigens (e.g., Pneumococcal Vaccine, Meningococcal Polysaccharide Vaccine)
57I	Multiple Vaccine/Multiple Antigen Preparations (e.g., Measles, Mumps, Rubella Vaccine; Diptheria, Tetanus, and Pertussis Vaccine)
57Y	Biologics & Licensed In-Vivo and In-Vitro Diagnostic Products Not Elsewhere Classified (N.E.C.)

Program/Assignment Codes: 42007

FIELD REPORTING REQUIREMENTS

All CBER import resources are planned under 42007. Report accomplishments under appropriate PAC. Planned resources Cover: PAC 42R833 (Entry Review), 41R824/42R824/45R824(Follow-Up to Refusals), 99R833 (Filer Evaluations) and any inspections needed for PAC 42007.

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PART I - BACKGROUND

The Center for Biologics Evaluation and Research regulates biological products, as well as certain drugs and devices. Current authority for this responsibility rests in the Public Health Service Act (PHS Act) and/or the Federal Food, Drug, and Cosmetic Act (FD&C Act).

CBER is responsible for ensuring:

- the safety of this nation's entire blood supply and the products derived from it;
- the production and approval of safe and effective vaccines, including childhood vaccines;
- an adequate and safe supply of allergenic products;
- the safety and efficacy of cellular and gene therapy products;
- the safety and efficacy of certain drugs and medical devices used in the testing and manufacture of biological products.

PART II - IMPLEMENTATION

This program provides information to assist reviewers and compliance officers in making admissibility decisions regarding all imported biological products, drugs, and devices regulated by CBER under section 351 of the PHS Act and/or under the FD&C Act.

A. Objectives

This is a continuing program to:

1. Determine if imported biological products, drugs, and devices regulated by CBER comply with the requirements of the FD&C Act, the PHS Act, and the regulations promulgated under these statutes. In particular:

    a. Determine if finished biological products, drugs, and devices regulated by CBER, including blood or blood components intended for transfusion, are the subject of an approved BLA, NDA, ANDA, PMA, a cleared 510(k), or an active IND or IDE.

    b. Determine if unfinished biological products, drugs, and devices regulated by CBER and intended for further processing or manufacture and distribution in the U.S. are the subject of an approved BLA, NDA, ANDA, PMA; a cleared 510(k); an active IND or IDE; or an FDA-approved short supply agreement and are adequately labeled.

    c. Determine if blood, blood components, Source Plasma, Source Leukocytes, or any component thereof that is declared as import-for-export has been approved by CBER for importation as required by Section 801(d)(4) of the FD&C Act and is adequately labeled.

    d. Determine if biological products, drugs, and devices regulated by CBER that are declared as import-for-export comply with Section 801(d)(3) of the FD&C Act and are adequately labeled.

2. Detain and/or refuse entry of imported biological products, drugs, and devices regulated by CBER that do not appear to comply with the applicable laws.

B. Program Management Instructions

1. Articles/Products Covered By This Program

The Center for Biologics Evaluation and Research (CBER) is the lead center for regulating biological products along

with certain drugs and devices. CBER has regulatory oversight over products belonging to the following classes:

- Antitoxins (e.g., botulism antitoxin) and Antivenins – products used in the treatment of venomous bites or stings (e.g., snake antivenins, spider antivenins) and antitoxins (e.g., botulism antitoxin);

- Vaccines -- products intended to induce or increase an antigen specific immune response for prophylactic or therapeutic immunization, regardless of the composition or method of manufacture (e.g., Influenza Virus Vaccine, Polio Virus Vaccine, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine (DTaP));

- Blood and blood components, including Source Plasma and Source Leukocytes;

- Plasma derived products (e.g., albumin, immunoglobulins, clotting factors, fibrin sealants, proteinase inhibitors), including recombinant and transgenic versions of plasma derivatives (e.g., clotting factors, blood substitutes);

- Blood bags with anti-coagulant (approved under NDA);

- Certain devices involved in the collection, processing, testing, manufacture and administration of licensed blood, blood components, and cellular products (e.g., blood bank reagents; viral marker test kits; blood bank software; red cell reagents; HLA reagents and instruments for automating such tests; stem cell concentration and separation systems; cord blood collection kits, processing systems, and storage containers); and

- All HIV Test Kits, whether they are used to diagnose patients or screen donors;

- Allergenic products, including diagnostic patch tests applied to the surface of the skin and used by physicians to determine the specific causes of contact dermatitis; and allergenic extracts – injectable products manufactured from natural substances known to elicit allergic reactions in susceptible individuals and used for the diagnosis and treatment of allergic diseases (e.g., allergic rhinitis ("hay fever"), food allergy);

- Cellular products, including products composed of human or animal cells (e.g., pancreatic islet cells for transplantation), or from physical parts of those cells (e.g., whole cells, cell fragments).

This program covers biological products, drugs, and devices regulated by CBER under section 351 of the PHS Act and/or

under the FD&C Act.

This program does NOT cover human cells, tissues, and cellular and tissue-based products (HCT/Ps) that are regulated solely under section 361 of the PHS Act. These "361 HCT/Ps" are covered under the Addendum to this Compliance Program (see http://www.fda.gov/cber/cpg/7341002tis.htm) (Addendum).

This program also does NOT cover the therapeutic biological products that were regulated by CBER but were transferred on June 30, 2003 to the Center for Drug Evaluation and Research (CDER). The categories of **t**herapeutic biological products transferred to CDER include**:**

- Monoclonal antibodies for in vivo use;
- Proteins intended for therapeutic use, including cytokines (e.g. interferons), enzymes (e.g. thrombolytics), and other novel proteins, except for those that are specifically assigned to CBER (e.g., vaccines and blood products). This category includes therapeutic proteins derived from plants, animals, or microorganisms, and recombinant versions of these products;
- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response); and
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo (growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo, for the purpose of being harvested for use in the production of a therapeutic cellular or blood product, may be regulated in combination with the therapeutic cellular or blood product, as appropriate); if there is any question about which Center is primarily regulating these products, contact CBER, OCBQ, DCM (see program contacts at Part VI.B.)).

A complete list of the therapeutic biological products that were transferred to CDER can be found at http://www.fda.gov/cber/transfer/transfprods.htm.

2. Import Sample Collections

If the district feels that a sample is warranted, prior to collection, contact CBER, OCBQ, DCM (See Part VI.B. for contact information).

3. Field Exams

Field exams are performed, as appropriate, in accordance with established procedures. See IOM 6.4.6 "Field Examination."

PART III- INSPECTIONAL

A. Entry Review under Section 801 of the FD&C Act

1. Affirmation of Compliance

An entry reviewer should consider whether the product appears to be licensed or approved by CBER or otherwise subject to regulation by CBER as a biological product, a drug, and/or a device.

FDA establishes Affirmation of Compliance (AofC) codes which provide FDA employees with information concerning the article offered for import. AofC codes assist FDA in making admissibility determinations. By using an AofC code, the filer affirms that the product identified in a FDA line meets the requirements for each code. Use of the AofC is voluntary, and may or may not provide for a more expeditious screening of the entry. If an AofC code is provided, the entry reviewer should verify that it is accurate.

A new system, MARCS Center Views, is now available on FDA's Intranet through ORA's Web Applications page, which should enable entry reviewers to verify AofC codes. To access the appropriate fields (e.g., "application number," "firm license number"), select the "CBER" tab once you have entered Center Views. Contact CBER, OCBQ, DCM (See Part VI.B. for contact information) if Center Views is not operational, if you are unable to verify the AofC codes, or if there are any other questions or concerns.

a. Licensed Biological Products

"Biological products" are defined in the PHS Act as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." Pursuant to Section 351(a) of the PHS Act, a biologics license must be in effect for any biological product introduced or delivered for introduction into interstate commerce (including imports).

The following AofC Codes may be applicable to licensed biological products:

- "STN" Submission Tracking Number

  The Affirmation Code is "STN"; the qualifier should be the submission tracking number issued by FDA for the licensed biological product identified in the FDA line. The submission tracking number is the biologics license application (BLA) number.

- "BLN" Biologics License Number

  The Affirmation Code is "BLN"; the qualifier should be the four digit U.S. Biologics License Number issued by FDA to the manufacturer of the biological product identified in the FDA line. The biologics license number is the U.S. license number (not the STN number).

b. Drug Products

The FD&C Act defines "drug" to mean "(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C)." Drug products, with the exception of biological products that have a BLA in effect, must have an approved application under section 505 of the FD&C Act.

Depending on the type of application (i.e., investigational, new drug, abbreviated new drug), the following AofC codes may be applicable:

- IND Investigational New Drug Application Number

  This affirmation and qualifier should be the Investigational New Drug Application Number issued by FDA (CDER, CBER) for the product identified in the FDA line. Investigational drugs are new drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs.

- NDA New Drug Application Number

  This affirmation and qualifier is the New Drug Application Number issued by FDA (CDER/CBER) for the product identified in the FDA line. A drug may be "new" if (1) it contains a newly developed chemical; (2) it contains a chemical or substance not previously used in medicine; (3) the drug has previously been used in medicine but not in the dosages or conditions for

which the sponsor now recommends its use; or (4) the drug has become recognized by qualified experts as safe and effective for its intended uses as a result of investigational studies but has not otherwise been used to a material extent or for a material time. A new drug cannot be commercially marketed in the U.S. unless it has been approved as safe and effective by the FDA based on a New Drug Application. The qualifier required is the NDA number assigned to the product by FDA.

- AND Abbreviated New Drug Application Number

This affirmation and qualifier should be the Abbreviated New Drug Application Number (ANDA) issued by FDA (CDER/CBER) for the human drug product identified in the FDA line. This number is the approval number in response to an abbreviated new drug application.

A list of currently approved new drug applications for drug products regulated by CBER can be located at http://www.fda.gov/cber/efoi/nda.htm.

c. Device Products

The FD&C Act defines "device" as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." CBER regulates the medical devices involved in the collection, processing, testing, manufacture and administration of licensed blood, blood components and cellular products. CBER also regulates all HIV test kits used both to screen donor blood, blood components and cellular products, and to diagnose, treat and monitor persons with HIV and AIDS.

Device products, with the exception of biological device products that have a BLA in effect, must have an approved premarket application, a cleared 510(k), or an investigational device exemption. A list of approved and cleared device products regulated by CBER can be located at

http://www.fda.gov/cber/efoi/pma.htm (for PMAs) and
http://www.fda.gov/cber/efoi/510k.htm (for 510(k)s).

The following AofC codes may be applicable to device products:

- PMA Device Premarket Approval Number

  The affirmation and qualifier should be the Device Pre-Market Approval Number issued by FDA (CDRH/CBER) for the product identified in the FDA line. Premarket approval can be required of devices if general controls are not sufficient to ensure safety and effectiveness and there is not enough information to establish a performance standard.

- PMN Device Pre-Market Notification Number (510(k))

  The affirmation and qualifier should be the Device Pre-Market Notification Number or 510(k) number issued by FDA (CDRH/CBER) for the product identified in the FDA Line. The foreign manufacturer has the primary responsibility, but can delegate to an initial distributor. A manufacturer must submit a pre-market notification when introducing a new device to the market, a device new to a particular manufacturer even though a similar device may already be marketed by another manufacturer, a device which is a modification of an existing product if the modification has significant impact on the safety and effectiveness of the device, or an old device with a major change in intended use.

- IDE Investigational Device Exemption Number

  The affirmation and qualifier should be the Investigational Device Exemption Number issued by FDA (CDRH/CBER) for the product identified in the FDA line. Devices that qualified experts use on human subjects, to conduct investigations of their safety and effectiveness, are considered investigational devices.

2. Import Alerts and Bulletins

The entry reviewer should determine if the foreign manufacturer or the biological product, drug, or device offered for import is listed on an active Import Alert or subject to an Import Bulletin; and, if so, follow the guidance in that Alert or Bulletin. Import Alerts can be found on the web at http://www.fda.gov/ora/fiars/ora_import_alerts.html; and Bulletins are located on the web at http://alpha.ora.fda.gov/www_fiars/files/import_bul_list.htm

1. CBER intends to communicate information, such as suspension or revocation of a U.S. license, through import alerts.

3. Review of Approval Status

a. Approved or Cleared Products

The entry reviewer should check to ensure that the foreign establishment holds an approved BLA, NDA, ANDA, PMA, or cleared 510(k) for the product. If the establishment does not hold the approved application or 510(k) clearance, the entry reviewer should refer the line to Compliance with a request for detention (DTR).

b. Investigational Products

The entry reviewer should check to ensure that the foreign establishment holds an IND or IDE in effect for the product. Center Views (CBER tab -- "application number" field) should be used to verify CBER INDs and IDEs. If Center Views is not operational for any reason, if the particular IND or IDE is not in the system, or if there are any questions or concern, reviewers should contact CBER, OCBQ, DCM (see program contacts at Part VI.B.). If the establishment does not have an IND or IDE in effect for its investigational products, the entry reviewer should refer the line to Compliance with a request for detention (DTR).[1]

c. Imported intermediates, active pharmaceutical ingredients, bulk substances, or other biologics for further manufacturing use

Unless the manufacturer is subject to the import-for-export provisions, as discussed in section d. below, intermediates, active pharmaceutical ingredients, bulk substances, or other biologics for further manufacturing may also use an AofC Code as described in sections 1.a. and 1.b. above. This is true even if the foreign manufacturer does not hold the approval, clearance, or investigational application for the final biological or drug product, as is the case with contract manufacturers. If there is any question about the link between the foreign manufacturer and the AofC Code provided, contact the importer to request clarification.

[1] An IND is not considered to be "in effect" for any investigational products that are subject to an investigation which has been placed on clinical hold. See 21 CFR 312.40(b)(1) and 312.42.

d. Import-for-Export Products

The AofC code for import-for-export products is: "IFE Import for Export." This affirmation allows for importation of violative articles (including drug and device components) under the import-for-export provisions of the FD&C Act. The article must be incorporated, by the initial owner or consignee, into a product for export; and the product must be exported from the United States by the initial owner or consignee, in accordance with the provisions of Sections 801(e) and 802 of the FD&C Act, or Section 351 of the PHS Act. No qualifier is required when using this AofC; however, quantity and value must be reported.

1. Drugs and Devices

The Import-for-Export provisions of Section 801(d)(3) of the FD&C Act permit a person to import unapproved or otherwise non-compliant drug components and device components as long as the imported item is further processed or incorporated into products that are exported from the U.S. Blood cells that meet the definition of HCT/Ps and are more than minimally manipulated are regulated as drug components and thus may be eligible for import-for-export under Section 801(d)(3). The entry reviewer should refer to the RPM, Chapter 9, Subchapter 9-15 "Import for Export" (http://www.fda.gov/ora/compliance_ref/rpm/chapter9/ch9.html) for handling these entries.

2. Blood, Blood Components, Source Plasma or Leukocytes or components, etc. thereof,

Section 801(d)(4) of the FD&C Act places additional limitations on the import-for-export of blood, blood components, Source Plasma, Source Leukocytes, or a component, accessory, or part thereof. These products are permitted importation under Section 801(d)(3) of the FD&C Act if the importation complies with licensing requirements of the PHS Act or if FDA permits the importation under appropriate circumstances and conditions through an FDA approved import-for-export request.

If shipments of blood, blood components, Source Plasma, or Source Leukocytes, etc., are identified as import-for-export, the entry reviewer should request a copy of the CBER approval letter from

the importer or contact CBER, OCBQ, DCM (See Contact information in Part VI.B.) to determine if approval has been granted pursuant to Section 801(d)(4). If CBER has not approved the importation, the entry reviewer should refer the line to Compliance with a request for detention (DTR). Charges and actions can be found in Part V.

e. Samples Offered for Import

1. Product Samples For Lot Release

Under 21 CFR 610.2, manufacturers may be required to submit to CBER samples from all lots of a licensed biological product, together with the protocols showing results of applicable tests when deemed necessary by the Director, CBER. For most biological products, CBER has required the submission of this information both in support of a license application and for continued lot release following product license application approval.

Samples of imported biological products that are offered for entry and consigned to the Sample Custodian at CBER pursuant to 21 CFR 610.2 (official release of requested samples) for lot release action should <u>not</u> be referred to Compliance with a request for detention (DTR).

2. Other Samples Consigned to the CBER Sample Custodian

If samples of products are offered for entry in order to be provided to the CBER Sample Custodian for reasons other than CBER's lot release program under 21 CFR 610.2 (e.g., premarket testing, pursuant to FDA request, etc.), the samples should <u>not</u> be referred to Compliance with a request for detention (DTR) as long as the consignee is the Sample Custodian at CBER.

3. Drug and Biologics Provisions Relating to Samples

Drugs (including biologics) intended solely for testing in vitro or laboratory research in animals may be shipped in accordance with 21 CFR 312.160. These drug products should be labeled:

"CAUTION: Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans."

In addition, 21 CFR 312.2(b)(2)(i) and 21 CFR 312.160 exempt blood grouping reagents, reagent red blood cells, and anti-human globulin intended for use in clinical investigations when the product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and the product is shipped in compliance with 21 CFR 312.160. If these products are shipped for investigational in-vitro diagnostic use, they must be labeled:

"CAUTION: Contains a biological product for investigational in vitro diagnostic tests only."

If the product appears to be inappropriately labeled, the entry reviewer should refer the line to Compliance with a request for detention (DTR). See Part V.A.3. for charges and detention procedures.

4. Device Provisions Relating to Samples

Devices (including biologics) intended for testing in vitro or in or on laboratory animals must be labeled in accordance with 21 CFR 812.5(c). The label must read:

"CAUTION—Device for investigational use in laboratory animals or other tests that do not involve human subjects."

Shipments of IVDs for other research or testing purposes are also permitted under 21 CFR 809.10(c)(2):

- For a product in the laboratory research phase of development, and not represented as an effective IVD, all labeling bears the statement, prominently placed:

  "For Research Use Only. Not for use in diagnostic procedures."

- For a product being shipped or delivered for product testing prior to full commercial marketing (for example, for use on specimens derived from humans to compare the usefulness of the product with other products or

procedures which are in current use or recognized as useful), all labeling bears the statement, prominently placed:

"For Investigational Use Only. The performance characteristics of this product have not been established."

If the product appears to be inappropriately labeled, the entry reviewer should refer the line to Compliance with a request for detention (DTR). See Part V.A.3. for charges and detention procedures.

f. Biological Specimens for Clinical Testing or for Basic Scientific Research

Biological specimens that are used only for testing in a clinical laboratory or for basic scientific research and that are not articles intended for the prevention, treatment, diagnosis, or cure of diseases, injuries, or conditions in human beings, are not considered to be biological products subject to licensure with FDA in accordance with Section 351(a) of the PHS Act, nor would they appear to be a drug or device as defined in Sections 201(g) and (h), respectively, of the FD&C Act (see "Importing Biological Specimens for Clinical Testing or Research Use Only – Frequently Asked Questions" at http://www.fda.gov/cber/faq/specimenfaq.htm). Thus, these specimens are not subject to FDA jurisdiction; and the filer should specify the entry is not subject to FDA regulation by "disclaiming" the entry (see section 6.2.3.5.1 of the Investigations Operations Manual).

If a shipment of one of these specimens is encountered, you may wish to consider whether the size and quantity appear to qualify as specimens for clinical testing or for basic scientific research. In most cases, a shipment of 1 to 30 tubes containing 10 cubic centimeters of plasma, serum, or blood would be considered samples for clinical testing. Districts also may want to verify that the consignees are clinical testing laboratories or research facilities actually engaged in clinical laboratory testing or laboratory research. (Some U.S. firms do have their own in-house testing and research laboratories, so the fact that it is being shipped to a biologics firm does not necessarily mean it is not going to a research facility.) If the District or entry reviewer suspects diversion, they should contact CBER, OCBQ, DCM (see program contacts at Part VI.B.).

g. Blood and Blood Components for Autologous Use Only

Entries of unlicensed human blood or blood components (e.g., whole blood, red blood cells, plasma) for autologous use only, should not be referred to compliance with a request for detention, provided the manufacturer of the product does not ship autologous blood products in interstate commerce on a routine or regular basis[2] and provided that the autologous blood products are for transfusion purposes only, have not been further processed or manipulated, and are labeled in accordance with the labeling regulations applicable to autologous blood, which are located at 21 CFR 606.121(i)(3),(4).

h. "Short Supply" Products

The short supply provisions of 21 CFR 601.22 allow an unlicensed establishment to conduct the initial and partial manufacturing of a biological product at places other than the establishment approved in the BLA, provided that all requirements of 21 CFR 601.22 are fulfilled.

Currently, products that may be supplied under 21 CFR 601.22 are:

- recovered plasma,
- red blood cells,
- snake venoms, and
- hymenopteran (bee) venoms.

In order to qualify as short supply products, these products must be for further manufacture only and not for final distribution. All manufacturers of products in short supply are required by regulation to be registered with FDA.

The entry reviewer should verify that a short supply agreement between the collection facility and the manufacturer of the final, licensed product is in effect prior to or at the time of shipment (see 21 CFR 601.22). This may be obtained by contacting the importer of record or the consignee. A short supply agreement is generally between the unlicensed initial or partial manufacturer and the manufacturer of the final, licensed product; short supply agreements are not valid if they are entered into between a plasma broker or broker(s) and the manufacturer of a final,

[2] See Ref. 7 for further discussion of routine or regular basis.

licensed product.

If there is no valid short supply agreement between the appropriate parties or the product is not correctly labeled, the entry reviewer should refer the line to Compliance with a request for detention (DTR) (see Part V.A.5., for charges).

i. Recovered Plasma and Serum Not The Subject of a Short Supply Agreement and Intended for Further Manufacture into Device Products Regulated Through a PMA or 510(k)

Recovered plasma and serum not subject to a short supply agreement and intended for further manufacture into device products regulated through a PMA or 510(k) (e.g., HIV rapid tests, in-vitro diagnostic reagents such as clinical chemistry controls) may be imported, provided that the recovered plasma or serum appears to have been manufactured in accordance with the applicable current good manufacturing practices, as required by 21 CFR 606[3], and provided that the immediate container is properly labeled as described in the labeling regulations (see 21 CFR 606.121 and 610.40).

Specifically, the container label should include:

- The proper name of the product [21 CFR 606.121(c)(1)];
- Name(s), address(es), and registration number(s) of establishment(s) collecting, preparing, labeling, or pooling the source material [21 CFR 606.121(c)(2)];
- Donor, Lot, or Pool number(s) [21 CFR 606.121(c)(3)];
- Expiration Date or, in the case of recovered plasma, date of collection of oldest material in the container [21 CFR 606.121(c)(4), (e)(5)];
- Volume of product [21 CFR 606.121(c)(6)];
- Recommended Storage Temperature [21 CFR 606.121(c)(7)];
- Name and volume of anticoagulant*(s)* [21 CFR 606.121(e)(1)];
- The statement, "This product may transmit infectious agents." [21 CFR 606.121(c)(9)];
- Statement "Caution: "Caution: For Further Manufacturing Use as a Component of, or to Prepare, a Medical Device." [21 CFR 610.40(c)(3)]. If the product is recovered

[3] If there is evidence of the appearance of a violation of Part 606, those facts may provide a basis for charging a violation of Section 501(a)(2)(B) of the FD&C Act. See Part V.B. for Section 501(a)(2)(B) charge language.

plasma and there is a reactive screening test for evidence of infection due to communicable disease agent(s) or is collected from a donor with a previous record of a reactive screening test, the recovered plasma must be labeled as appropriate: "Caution: For Further Manufacturing Use as a Component of a Medical Device for Which There are No Alternative Sources" or "Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents for Which There are No Alternative Sources." [21 CFR 606.121(e)(5)(ii); 21 CFR 610.40(h)(2)(ii)(E)]

- For recovered plasma not meeting the requirements for manufacture into licensable products, the statement: "Not for Use in Products Subject to License Under Section 351 of the Public Health Service Act." [21 CFR 606.121(e)(5)(iii)]

If the product is inappropriately labeled, the entry reviewer should refer the line to Compliance with a request for detention (DTR) (see Part V.A.5. for charges).

4. Other Agencies' Requirements

On occasion, a product offered for import may be held or detained due to another agency's requirements. For example, a product may be held or detained because it needs an Etiological Agent Import Permit from the Centers for Disease Control and Prevention (see http://www.cdc.gov/od/eaipp/) or an Animal Health or Veterinary Biologics Import Permit from the Animal and Plant Health Inspection Service in the United States Department of Agriculture (see http://www.aphis.usda.gov/permits/). If the District discovers that a product is being held because it needs such a permit, the entry reviewer should advise that these are not FDA's requirements but are those of another agency and that is the company's responsibility (not FDA's) to obtain such a permit.

B. Documents That May Be Requested

If no Affirmation of Compliance is provided, or if questions relating to the entry arise, the entry reviewer may request relevant documents that provide sufficient information to make an admissibility decision. Documents that may be requested include, for example:

- The FDA approval (approved BLA, NDA, ANDA, PMA), clearance (cleared 510(k)), or active investigational approval or exemption (active IND or IDE) for an

approved, cleared, or investigational product.
- Labeling for the product
- Short supply agreement
- Import-For-Export approval letter under Section 801(d)(4) (where applicable)

If you request labeling, standards for labeling of biological products are found in several places, including:

- 21 CFR 610 subpart G provides general labeling standards for biological products. Additional labeling requirements can be found in 21 CFR 610.40.
- 21 CFR 606.121 and 21 CFR 606.122 specify labeling requirements for blood and blood components, except that:
  - 21 CFR 640.70, 640.74(b)(4), and 640.76 specify labeling requirements for Source Plasma.
- 21 CFR 640.84 specifies labeling requirements for albumin.
- 21 CFR 640.94 specifies labeling requirements for plasma protein fraction (human).
- 21 CFR 660.28 specifies labeling requirements for blood grouping reagents.
- 21 CFR 660.35 specifies labeling requirements for reagent red blood cells.
- 21 CFR 660.2(c) specifies labeling requirements for antibody to Hepatitis B Surface Antigen.
- 21 CFR 660.45 specifies labeling requirements for Hepatitis B Surface Antigen.
- 21 CFR 660.55 specifies labeling requirements for anti-human globulin.

21 CFR 201 specifies the labeling requirements for drug products. Labeling requirements for investigational new drugs are set out at 21 CFR 312.6.

21 CFR Sections 801 and 809 specify the labeling requirements for medical devices.

Contact CBER, OCBQ, DCM (see program contacts at Part VI.B.) if you have further questions concerning the labeling of the entry.

C. Special Circumstances

1. Counterfeit Products

If you suspect that a product offered for import is counterfeit, contact CBER, OCBQ, DCM (see program contacts at Part VI.B.) to establish an appropriate plan of action.

2. American Goods Returned

If a product offered for import has been returned ("American Goods Returned"), rejected, or has a complaint file, the district should carefully review that entry to determine the reason for the return, rejection, or complaint. In addition, products that are identified as "American Goods Returned" should travel with documentation demonstrating that the product was kept under the appropriate storage conditions while in foreign storage and during shipment back to the United States. Note that if the product is a drug, section 801(d)(1) of the FD&C Act applies, and the product must be imported by the U.S. manufacturer.

In your judgment, if there is reason to believe that an appearance of violation may exist, then consult with CBER for assistance, if needed. Goods should be detained with the appropriate charge when they appear violative. If there are any questions, contact CBER, OCBQ, DCM (see program contacts at Part VI.B.).

3. Medical Emergency

Section 801(d)(2) of the FD&C Act permits the Secretary to authorize the importation of a drug, which would otherwise be prohibited, if the drug is required for emergency medical care. Districts should use discretion in detaining a product offered for import if its use is required for a medical emergency.

D. Physical Examination of Articles

Should opening and examining a shipping container be deemed necessary, latex gloves should be worn since the possibility of leaky containers containing biohazardous materials exists. Other protective clothing or glasses should be considered in accordance with OSHA regulations. Refer to section 1.5.1 of the Investigations Operations Manual.

PART IV - ANALYTICAL

If sample collection is necessary, specific instructions will be provided, including the laboratory or laboratories to which the sample should be sent. Consult with CBER program contacts identified in Part VI, ***before*** collecting samples for agency analysis, except for documentary samples for interstate commerce (collect a documentary sample in accordance with IOM 4.1.4.2, "Documentary Samples" to support regulatory/administrative action). When sample collection is necessary, CBER will notify the Division of Field Science, Office of Regional Operations/ORA.

If samples are to be evaluated by CBER, contact the CBER Sample Custodian (301-594-6517) before shipping any samples. No one is

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-235
5516 Nicholson Lane, Building B, Room 113
Kensington, MD 20895

Collect any samples of a potentially bio-hazardous nature in accordance with IOM 1.5.5.

Original results of analyses will be forwarded to the home district, with a copy to CBER, OCBQ, DCM, HFM-624. Investigators should designate on the FDA-464, Collection Report, to whom the sample results should be forwarded.

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

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

A. CHARGES[4]

1. Approved/Licensed and Investigational Biological Products

A product offered for import should be detained if the foreign establishment does not hold an approved BLA, NDA, ANDA, PMA, a cleared 510(k), or does not hold an IND or IDE in effect for the product that is described in the entry (see limited exception in Part III.A.3.c. for imported intermediates, active pharmaceutical ingredients, bulk substances, or biologics for further processing), or the product does not otherwise appear to be in compliance with the laws. Consider the type and the intended use of the biological product.

If the product appears to be a biological product, include the following statement on the Notice of FDA Action:

- "Because the article appears to be a biological product for which a biologics license is not in effect under Section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)), the article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that it appears to be a new drug within

[4] These charges are not all-inclusive. For example, should an entry reviewer encounter an appearance of adulteration, e.g., for failure to comply with current good manufacturing practice, see Section 501(a)(2)(B) charge under detention in Part V.B.

the meaning of Section 201(p) of the FD&C Act (21 U.S.C. 321(p)) without an approved new drug application in effect, as required by Section 505 of the FD&C Act (21 U.S.C. 355), or a class III device which does not have an approved application for premarket approval in effect pursuant to Section 515(a) of the FD&C Act (21 U.S.C. 360e(a)) or an approved application for an investigational device exemption under Section 520(g) of the FD&C Act (21 U.S.C. 360j(g))." **[OASIS Code = NO LICENSE]**

If the product appears to be a drug, include the following statement on the Notice of FDA Action:

- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3) in that it appears to be a new drug within the meaning of Section 201(p) of the FD&C Act (21 U.S.C. 321(p)) without an approved new drug application in effect, as required by Section 505 of the FD&C Act (21 U.S.C. 355)." **[OASIS Code = UNAPPROVED]**

If the product appears to be a device, include the following statement on the Notice of FDA Action:

- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that it appears to be a class III device which does not have an approved application for premarket approval in effect pursuant to Section 515(a) of the FD&C Act (21 U.S.C. 360e(a)) or an approved application for an investigational device exemption under Section 520(g) of the FD&C Act (21 U.S.C. 360j(g))." **[OASIS Code = NO PMA]**

2. Import-for-Export Products

Detain all products identified as import-for-export if they do not comply with sections 801(d)(3), or (4) of the FD&C Act. Consider the type and the intended use of the product.

If the product appears to be a biological product, include the following statement on the Notice of FDA Action:

- "Because the article appears to be a biological product for which a biologics license is not in effect under Section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)), the article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C.

381(a)(3)) in that it appears to be a new drug within the meaning of Section 201(p) of the FD&C Act (21 U.S.C. 321(p)) without an approved new drug application in effect, as required by Section 505 of the FD&C Act (21 U.S.C. 355), or a class III device which does not have an approved application for premarket approval in effect pursuant to Section 515(a) of the FD&C Act (21 U.S.C. 360e(a)) or an approved application for an investigational device exemption under Section 520(g) of the FD&C Act (21 U.S.C. 360j(g))." **[OASIS Code =NO LICENSE]**

If the product appears to be a drug, include the following statement on the Notice of FDA Action:

- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that it appears to be a new drug within the meaning of Section 201(p) of the FD&C Act (21 U.S.C. 321(p)) without an approved new drug application in effect, as required by Section 505 of the FD&C Act (21 U.S.C. 355)." **[OASIS Code = UNAPPROVED]**

If the product appears to be a device, include the following statement on the Notice of FDA Action:

- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that it appears to be a class III device which does not have an approved application for premarket approval in effect pursuant to Section 515(a) of the FD&C Act (21 U.S.C. 360e(a)) or an approved application for an investigational device exemption under Section 520(g) of the FD&C Act (21 U.S.C. 360j(g))." **[OASIS Code = NO PMA]**

3. Samples

Detain all biological products identified "For Research Use Only" or "For Testing Only", if it appears that the consignee is not a test laboratory or research facility engaged in clinical testing or laboratory research. Consider the type and the intended use of the product.

If the product appears to be a biological product, include the following statement on the Notice of FDA Action:

- "Because the article appears to be a biological product for which a biologics license is not in effect under Section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)), the article is subject to refusal of

admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that it appears to be a new drug within the meaning of Section 201(p) of the FD&C Act (21 U.S.C. 321(p)) without an approved new drug application in effect, as required by Section 505 of the FD&C Act (21 U.S.C. 355), or a class III device which does not have an approved application for premarket approval in effect pursuant to Section 515(a) of the FD&C Act (21 U.S.C. 360e(a)) or an approved application for an investigational device exemption under Section 520(g) of the FD&C Act (21 U.S.C. 360j(g))." **[OASIS Code = NO LICENSE]**

If the product appears to be a drug, include the following statement on the Notice of FDA Action:

- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that it appears to be a new drug within the meaning of Section 201(p) of the FD&C Act (21 U.S.C. 321(p)) without an approved new drug application in effect, as required by Section 505 of the FD&C Act (21 U.S.C. 355)." **[OASIS Code = UNAPPROVED]**

If the product appears to be a device, include the following statement on the Notice of FDA Action:

- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that it appears to be a class III device which does not have an approved application for premarket approval in effect pursuant to Section 515(a) of the FD&C Act(21 U.S.C. 360e(a)) or an approved application for an investigational device exemption under Section 520(g) of the FD&C Act (21 U.S.C. 360j(g))." **[OASIS Code = NO PMA]**

In addition, if these products appear to be incorrectly labeled, include one of the following statements on the Notice of FDA Action:

- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that the article appears to be misbranded because its labeling appears to be false or misleading in violation of Section 502(a) of the FD&C Act (21 U.S.C. 352(a))." **[OASIS Code = FALSE]**
- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that the article

appears to be misbranded because its labeling appears to fail to bear adequate directions for use in violation of Section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1))." **[OASIS Code = DIRECTIONS]**

4. Short Supply Products

Detain products purporting to be "short supply" products if there does not appear to be a short supply agreement in effect, or if the products do not appear to be properly labeled.

If there does not appear to be a short supply agreement and the product is subject to licensure, the product is an unapproved new drug and should be charged in accordance with Part V.A.1. If the product is intended for further manufacture into a finished product that is not subject to licensure, see Part V.A.6. below.

Products, including blood and blood components, intended for further manufacture into licensed biological products, except for Recovered Plasma, must be labeled "Caution: For Manufacturing Use Only" (see 21 CFR 606.121(c)(11)). Recovered Plasma must be labeled in accordance with 21 CFR 606.121(e)(5)(ii). Recovered Plasma for further manufacture into an injectable product must be labeled, "Caution: For Manufacturing Use Only". Recovered Plasma for further manufacture into a noninjectable product must be labeled, "Caution: For Use in Manufacturing Noninjectable Products Only".

If the product does not appear to be correctly labeled, include one of the following statements on the Notice of FDA Action:

- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that the article appears to be misbranded because its labeling appears to be false or misleading in violation of Section 502(a) of the FD&C Act (21 U.S.C. 352(a))." **[OASIS Code = FALSE]**
- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that the article appears to be misbranded because its labeling appears to fail to bear adequate directions for use in violation of Section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1))." **[OASIS Code = DIRECTIONS]**

5. Recovered Plasma and Serum Not The Subject of a Short Supply Agreement and Intended for Further Manufacture

into unlicensed device products

Detain all recovered plasma and serum that is not subject to a short supply agreement and that is intended for further manufacture into unlicensed device products if the blood and blood components do not appear to be manufactured in accordance with the current good manufacturing practices in 21 CFR 606 and/or do not appear to be labeled in accordance with the labeling requirements in 21 CFR 606.121.

If the products do not appear to be manufactured in accordance with the current good manufacturing practices in 21 CFR 606 such that these products appear to be adulterated, include the following statements on the Notice of FDA Action:

- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that the article appears to be a drug and the methods used in, or the facilities and controls used for, its manufacture, processing, packing, or holding do not appear to conform to or do not appear to be operated or administered in conformity with current good manufacturing practice in violation of Section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B))." [**OASIS Code = DRUG GMPS**]

If the products do not appear to be properly labeled, include one of the following statements on the Notice of FDA Action:

- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that the article appears to be misbranded because its labeling appears to be false or misleading in violation of Section 502(a) of the FD&C Act (21 U.S.C. 352(a))." **[OASIS Code = FALSE]**
- "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that the article appears to be misbranded because its labeling appears to fail to bear adequate directions for use in violation of Section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1))." **[OASIS Code = DIRECTIONS]**

B. ACTIONS

For violative biological products, drugs, and devices regulated by CBER under section 351 of the PHS Act and/or under the FD&C Act that are still in import status, the available enforcement options include:

Detention	If the product appears to be a licensed biological product, include the following statement on the Notice of FDA Action: • "Because the article appears to be a licensed biological product for which a biologics license is not in effect under Section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)), the article appears to be subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that it appears to be a new drug within the meaning of Section 201(p) of the FD&C Act (21 U.S.C. 321(p)) without an approved new drug application in effect, as required by Section 505 of the FD&C Act (21 U.S.C. 355), or a class III device which does not have an approved application for premarket approval in effect pursuant to Section 515(a) of the FD&C Act (21 U.S.C. 360e(a)) or an approved application for an investigational device exemption under Section 520(g) of the FD&C Act (21 U.S.C. 360j(g))." **[OASIS Code = NO LICENSE]** If the product appears to be a new drug, include the following statement on the Notice of FDA Action: • "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that it appears to be a new drug within the meaning of Section 201(p) of the FD&C Act (U.S.C. 321(p)) without an approved new drug application in effect, as required by Section 505 of the FD&C Act (21 U.S.C. 355)." **[OASIS Code = UNAPPROVED]** If the product appears to be a device, include the following statement on the Notice of FDA Action: • "The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that it appears to be a class III device which does not have an approved application for premarket approval in effect pursuant to Section 515(a) of the FD&C Act (21 U.S.C. 360e(a)) or an approved application for an investigational device exemption under Section 520(g) of the FD&C Act (21 U.S.C. 360j(g))." **[OASIS Code = No PMA]** If the product appears to be in violation of CGMPs, include the following statement on the Notice of FDA Action: • "The article is subject to refusal of admission

	pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that the article appears to be a drug and the methods used in, or the facilities and controls used for, its manufacture, processing, packing, or holding do not appear to conform to or do not appear to be operated or administered in conformity with current good manufacturing practice in violation of Section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)).” [**OASIS Code = DRUG GMPS**] If the product appears to be mislabeled, include the following statement(s), as applicable, on the Notice of FDA Action: • “The article is subject to refusal of admission pursuant to Section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that the article appears to be misbranded because its labeling appears to be false or misleading in violation of Section 502(a) of the FD&C Act (21 U.S.C. 352(a)).” **[OASIS Code = FALSE]** • “The article is subject to refusal of admission pursuant to section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381(a)(3)) in that the article appears to be misbranded because its labeling appears to fail to bear adequate directions for use in violation of Section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)).” **[OASIS Code = DIRECTIONS]**
Refusal	Refusal of biological products, drugs, and devices based on the appearance of violations as described in section 801(a) of the FD&C Act. Product can be re-exported or destroyed.
DWPE – Import Alert	Districts may recommend DWPE whenever there is information that would cause future shipments of biological products, drugs, or devices offered for entry to appear violative under Section 351 of the PHS Act or the FD&C Act. See RPM Chapter 9, Subchapter, Detention Without Physical Examination, regarding procedures for DWPE and other pertinent guidance on entry control procedures. Recommendations for DWPE should be referred to CBER, Division of Case Management, HFM-624, through ORA/ORO, Division of Import Operations and Policy, HFC-170.
Warning Letters	Please consult with CBER (see program contacts, part VI.C.)
Bond Actions	Bond actions may be initiated by U.S. Customs and Border Protection (CBP) when an entry is distributed prior to FDA release and cannot be redelivered, or when an article has been detained and refused and the

	article is not destroyed or exported in accordance with the requirements of the law. Districts should work closely with the responsible CBP office. See IOM 6.2.7.11 Bond Actions and RPM Chapter 9, Subchapter Bond Actions.
Custom Seizures	CBP has seizure authority over merchandise whose importation or entry is subject to any restriction or prohibition which is imposed by law relating to health or safety and may be seized in accordance with 19 USC 1595a(c)(2)(A). Provide CBP with charge code, pertaining to health or safety.

PART VI – REFERENCES/PROGRAM CONTACTS

A. References

1. Investigations Operations Manual (IOM), Chapter 6 – Imports (http://www.fda.gov/ora/inspect_ref/iom/contents/ch6_toc.html).

2. FIARS: Import Alerts Listing (http://www.fda.gov/ora/fiars/ora_import_alerts.html)

3. Regulatory Procedures Manual, Chapter 9 - Import Operations/Actions (http://www.fda.gov/ora/compliance_ref/rpm/default.htm).

4. Compliance Policy Guidance Manual, Chapter 2 – Biologics(http://www.fda.gov/ora/compliance_ref/cpg/default.htm)

5. "Establishments and Products Licensed Under Section 351 of the Public Health Service Act" See http://www.fda.gov/cber/establish.htm for a listing of FDA licensed products. Also see http://www.fda.gov/cber/products/testkits.htm for a listing of FDA approved/licensed in vitro diagnostic test kits.

6. Memo to All Registered Blood Establishments, Dated February 12, 1990, Subject: Autologous Blood Collection and Processing Procedures (See http://www.fda.gov/cber/bldmem/021290.pdf).

B. Program Contacts

For general import compliance issues and U.S. license information contact:

CBER/OCBQ ORA/ORO

Division of Case Management.
HFM-610

Phone: (301) 827-6201
Fax: (301) 594-0940
Kimberly Cressotti: (301) 827-6214
Diane Alexander: (301) 827-6226
Robert Sausville: (301) 827-6205

Division of Import Operations and Policy,
HFC-172
Phone: (301) 443-6553
Fax: (301) 594-0413
Stella Notzon
Nawab Siddiqui

ORA/ORO
Division of Field Science
HFC-141
Phone:(301) 827-1032
Larry D'Hoostelaere

PART VII - CENTER RESPONSIBILITY/PROGRAM EVALUATION

CBER, OCBQ, will work cooperatively with ORA, and the Biological Products Field Committee, concerning imported biological products, drugs, and devices covered under this compliance program.

The ORA annual workplan, developed by CBER and ORA, provides overall resource allocations. However, in some circumstances, FDA may examine and/or sample the product offered for import, which may result in unplanned import activities taking more or less time than estimated in the workplan. In such a circumstance, the Center should be contacted for further guidance.

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.

CBER and ORA jointly coordinate activities to achieve industry compliance with applicable laws, and regulations.

CBER, OCBQ, will continue to use accomplishment data from the ORA OASIS, ORADSS Import Systems, and Field Accomplishment and Compliance Tracking System (FACTS), requests for policy decisions/clarification received from the public or the industry, and input from CBER scientific and product experts to aid industry and the field in the development of a consistent import compliance program that meets all applicable regulations.

Attachment A: Explanation of Terms Used in This Program

Autologous Blood - Blood collected from an individual and intended for reinfusion into that same individual. This product must be licensed in accordance with section 351 of the PHS Act when the manufacturer ships interstate or imports on a routine or regular basis (For additional guidance on Autologous Blood Collection and Processing Procedures, see Memorandum to All Blood Establishments, dated February 12, 1990, at http://www.fda.gov/cber/bldmem/021290.pdf).

Biologics License Application (BLA) - To obtain a biologics license under section 351 of the Public Health Service Act for any biological product, a manufacturer submits a biologics license application under 21 CFR 601.2, which requires a demonstration that the manufactured product meets the prescribed requirements of safety, purity, and potency.

Investigational Device Exemption (IDE) - Once in effect, an IDE allows the shipment of an unapproved device for use in a clinical investigation. 21 CFR 812 are the IDE regulations.

Investigational New Drug Application (IND) - Once in effect, an IND allows the shipment of an unapproved new drug for use in a clinical investigation. 21 CFR 312 are the IND regulations.

In Vitro Diagnostic products (IVDs)(21 CFR 809.3(a)) - Reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. IVDs are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in Section 201(h) of the FD&C Act and also may be biological products subject to section 351 of the PHS Act.

Manufacture (21 CFR 600.3(u)) - All steps in the propagation or manufacture and preparation of products and includes, but is not limited to, filling, testing, labeling, packaging, and storage by the manufacturer.

Manufacturer (21 CFR 600.3(t))- Any person or legal entity engaged in the manufacture of a product subject to license under the PHS Act as well as any person or legal entity that is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

New Drug Application (NDA) - A new drug application means an application submitted for FDA approval under Section 505 of the FD&C Act and 21 CFR 314.50.

Premarket Approval Application (PMA) - An application for FDA approval to distribute a class III medical device submitted

pursuant to section 515 of the FD&C Act and 21 CFR 814, including all information submitted with or referenced therein.

Premarket Notification (510(k)) – A premarket notification application that is submitted to the FDA pursuant to section 510(k) of the FD&C Act and 21 CFR 807 to demonstrate that the medical device is substantially equivalent to a legally marketed Class I or Class II device.

Recovered Plasma - Human plasma derived as a by-product from single units of whole blood, or as a by-product in the preparation of blood components from whole blood collection. (Recovered plasma is distinguished from Source Plasma by the mode of collection and the requirements for storage, pooling, dating and labeling of the product.)

Short Supply - Under 21 CFR 601.22, a licensed biologic manufacturer may obtain certain materials that are manufactured at unlicensed facilities when the following conditions are met: (1) manufacturing at the unlicensed facility will be limited to the initial and partial manufacturing of a product for shipment solely to the licensee; (2) the unlicensed manufacturer is registered with FDA in accordance with registration and listing provisions in 21 CFR parts 207 and 607; (3) the licensed product is in short supply due either to peculiar growth requirements or scarcity of the source organism required for manufacturing; and (4) the licensed manufacturer can assure that, through inspections, testing, or other arrangements, the product made at the unlicensed facility will be made in full compliance with applicable regulations.

Source Leukocytes – Human blood leukocytes intended for further manufacture and collected specifically by leukapheresis. Source leukocytes are subject to licensure under the provisions of Section 351 of the PHS Act.

Source Plasma (21 CFR 640.60) ---The fluid portion of human blood collected by plasmapheresis (which is described in 21 CFR 640.65 and 606.3(e)).