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: Major Update due to Automated Commercial Environment/International Trade Data System (ACE/ITDS) implementation

October 1, 2018

Completion Date: October 1, 2022

Product Codes:

Product Codes with associated Agency Processing Codes and corresponding Commodity Subtypes and Examples **Government Agency Program Code & Commodity: BIO - Biologics**		
Product Codes	Agency Processing Codes & Corresponding Commodity Sub-types	Examples of CBER Regulated Products
57A	BDP Blood Derivatives	Antitoxins (e.g., Botulism Antitoxin) and Antivenins (e.g., snake, scorpion, spider)
57B	VAC Vaccines	Immunization Toxoids (e.g., Diphtheria Toxoid, Tetanus Toxoid)

Product Codes with associated Agency Processing Codes and corresponding Commodity Subtypes and Examples **Government Agency Program Code & Commodity: BIO - Biologics**		
Product Codes	Agency Processing Codes & Corresponding Commodity Sub-types	Examples of CBER Regulated Products
57C	VAC Vaccines	Viral Vaccines (e.g., Rabies, Yellow Fever, Small Pox, Influenza Vaccines)
57D	BLO Blood & Blood Products	Blood & Blood Components, single donor & pheresis (e.g., Whole Blood (Human), Red Blood Cells (Human), Source Plasma (Human))
57E	ALG Allergenics	In-Vivo Diagnostic Products (e.g., Tuberculin PPD (skin test))
57G	ALG Allergenics	Allergenic Products (e.g., Allergenic Extracts, animal allergens, venoms (bee, wasp, hornet, yellow jacket))
57H	VAC Vaccines	Bacterial Vaccines/Antigens (e.g., Pneumococcal Vaccine, Meningococcal Polysaccharide Vaccine, Bacterial Antigen (No U.S. Standard Potency)
57I	VAC Vaccines	Multiple Vaccine/Multiple Antigen Preparations (e.g., Measles, Mumps, Rubella Vaccine; Diphtheria, Tetanus, and Pertussis Vaccine)
57M	CGT Cell & Gene Therapy	Umbilical cord blood stem cells, peripheral blood stem cells, Lymphocytes (Donor Lymphocytes for Infusion, T Cells)
57N	CGT Cell & Gene Therapy	Cell Therapies, Gene Therapies (vectors, genetically modified cells)

Product Codes with associated Agency Processing Codes and corresponding Commodity Subtypes and Examples **Government Agency Program Code & Commodity: BIO - Biologics**		
Product Codes	Agency Processing Codes & Corresponding Commodity Sub-types	Examples of CBER Regulated Products
57U	BDP Blood Derivatives	Blood Derivatives (e.g., Albumin, Immune Globulin, Factor XIII Concentrate, Fibrin Sealant))
57V	BLD Licensed Devices	In-Vitro Diagnostic Products (e.g., Hepatitis B Surface Antigen and Human Immunodeficiency Virus types 1 & 2, Reagent Red Blood Cells, Blood Grouping Reagents)
57W	VAC Vaccines	Immunomodulators (e.g., Whipworm, Hookworm)
57Y	PVE Plasma Volume Expanders	Plasma Volume Expanders (e.g., Dextran),
57Y	BBA Blood Bag with Anti-coagulant	Biological In-Vivo and In-Vitro Diagnostic Products Not Elsewhere Classified (N.E.C.)

Program/Assignment Codes: 42007 (Imported CBER-Regulated Products)

FIELD REPORTING REQUIREMENTS

All CBER import resources are planned under 42007. Report accomplishments under appropriate PAC. Planned resources cover: PAC 42R833(OASIS ELECTRONIC ENTRY REVIEW – BIOLOGICS), 41R824/42R824/45R824 (Follow-Up to Refused Import Entries), 99R833 (Import Filer Evaluations) under PAC 42007.

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PART I - BACKGROUND

The Center for Biologics Evaluation and Research (CBER) regulates biological products, as well as certain drugs and devices. Current authority for this responsibility rests in the Public Health Service (PHS) Act and/or the Federal Food, Drug, and Cosmetic (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.
- the safety and efficacy of certain of Human Cells, Tissues and Cellular and Tissue-based products.

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PART II - IMPLEMENTATION

This program provides information to assist FDA import entry 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. Including, but not limited to:
    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 and are adequately labeled. 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, as appropriate, and are adequately labeled.

b. 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.

c. 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. Administratively destroy any refused drugs regulated by CBER that are valued at $2500 or less (or such higher amount that the Secretary of the Treasury may set by regulation) (21 CFR 1.94).

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); [BDP]
- 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)); [VAC]
- Blood and blood components, including Source Plasma and Source Leukocytes; [BLO]
- 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); [BDP], [PVE]
- Blood bags with anti-coagulant (approved under NDA); [BBA]
- Certain devices involved in the collection, processing, testing, manufacture and administration of licensed blood, blood components,

and human cells, tissues, and cellular and tissue-based products (HCT/Ps) (e.g., blood bank reagents; viral marker test kits; red cell reagents; [BLD]

- HIV Test Kits used to screen donors; [BLD]
- 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); [ALG] and
- Human cell therapy are products that FDA has determined do not meet all of the criteria in 21 CFR 1271.10(a) and are regulated as drugs and/or biological products. Cellular immunotherapies, cancer vaccines, and other types of both autologous and allogenic cells for certain therapeutic indications, including hematopoietic stem cells derived from peripheral and cord blood fall under this category. Products that introduce genetic material into a person's DNA to replace faulty or missing genetic material, thus treating a disease or abnormal medical condition also fall in this category; [CGT]

  Examples include:

  - Autologous cultured chondrocytes
  - Autologous cellular immunotherapy
  - Gene therapy products

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 [XEN, HCT]

(see https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/CompliancePrograms/UCM095253.pdf))

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).

A complete list of the therapeutic biological products that were transferred to CDER can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelope

dandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm.

2. Import Sample Collections

   If an import division decides that obtaining a sample is appropriate, that division should contact CBER, Office of Compliance and Biologics Quality (OCBQ), Division of Case Management (DCM) prior to initiating collection of the sample. (See Part VI.B. for program contact information).

3. Field Exams

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

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PART III- INSPECTIONAL

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

As of July 23, 2016, the Automated Commercial Environment/International Trade Data System (ACE/ITDS) became the electronic data interchange system authorized by U.S. Customs and Border Protection (CBP) for processing of FDA-regulated imports in the United States. FDA issued a final rule on November 29, 2016, which became effective on December 29, 2016 (81 FR 85854). This rule established requirements for certain key data to be submitted, at the time of entry, as part of the electronic import entry in ACE.

When filing an entry in ACE, the filer must submit the following information (21 CFR 1.72):

(a) Product identifying information for the article. This consists of:

   a. FDA Country of Production

   b. Complete FDA Product Code

   c. Full Intended Use Code

(b) Importer of record contact information, which is the telephone and email address of the importer of record.

FDA Supplemental Guidance for ACE/ITDS, available on the CBP website or from this FDA website link, provides details on the submission of data for articles regulated by each Center (see

https://www.fda.gov/forindustry/importprogram/entryprocess/importsystems/ucm456276.htm.

Intended Use Codes

Intended Use Codes (IUC) provide a consistent, systematic approach to collection of certain intended use information about articles being imported or offered for import into the United States. The regulations at 21 CFR 1.72(a)(3) require that a full IUC be submitted in ACE at the time of entry for each FDA-regulated article that is being imported or offered for import into the United States.

1. Affirmation of Compliance

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

   FDA uses Affirmation of Compliance (AofC) codes for filers to provide FDA employees with information concerning the article offered for import. The submission of AofC codes and/or associated data assists FDA in making admissibility determinations. For certain AofC codes, the filer affirms that the product identified in a FDA line meets FDA requirements for importation of that article. Other AofC codes require certain data (qualifiers) to be submitted with the code. Submission of the AofC code and/or data (qualifiers) was voluntary in the CBP's previous Automated Commercial System (ACS). However, with the implementation of ACE/ITDS and the final rule (21 CFR 1.72, and 21 CFR 1.78), FDA requires submission of certain data elements (including AofC) for import of CBER-regulated products. When the AofC code is provided, the entry reviewer should verify that the code and the data (qualifiers) are accurate. for that article.

   Center Views is available on FDA's Intranet through ORA's Production Applications page, which should enable entry reviewers to verify AofC codes. To access the appropriate fields (e.g., "application number," "firm license number"), the entry reviewers should select the "CBER" tab once in Center Views. Contact CBER, OCBQ, DCM (see Part VI.B. for program contact information) if Center Views is not operational, or if there are questions about verifying the AofC codes.

   a. Licensed Biological Products

      "Biological products" are defined in section 351(i) of PHS Act as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), 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 to be introduced or delivered for introduction into interstate commerce (including imports).

The Submission Tracking Number (STN) and/or the Biologics License Number (BLN) AofC codes are required for licensed biological products (21 CFR 1.78 (c)). This information is transmitted to FDA using the following AofC Codes:))

- "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 six digit 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 section 201(g) 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, new drug, abbreviated new drug, the following AofC codes may be applicable:

- IND Investigational New Drug Application Number (21CFR 1.78 (f))

  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.

- DA is the new AofC that applies to both the New Drug Application and Abbreviated New Drug Application Number (NDA and ANDA) (21CFR 1.78 (e)).

    - For NDAs regulated by CBER, DA AofC followed by the prefix BN and qualifier refers to 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 (21 CFR 1.74).

- For ANDAs regulated by CBER, DA followed by the prefix BA and qualifier refers to 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 (21 CFR 1.74).

- REG AofC followed by the Drug Registration Number is required for importation of NDAs and ANDAs (21CFR 1.78 (d)).

A list of currently approved new drug applications for drug products regulated by CBER can be located at http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/NewDrugApplicationsNDAs/UCM149972.pdf .

c. Device Products

The FD&C Act section 201(h) 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.

In the ACE/ITDS environment there has been a major change in the processing of CBER regulated device imports. Licensed devices will continue to come under the Biologics Industry Code, but the Investigational Devices (IDEs) and devices regulated under PMA and 510k have been removed from the Biologics Commodity data section, and will now come under the Medical Device Industry Codes and processed under the Center for Devices and Radiological Health (CDRH) import processes. PM# is the new Affirmation of Compliance Code for the unlicensed devices (PMAs and PMNs).

The processing of the CBER regulated devices is outlined below.

Licensed Devices:

Licensed devices should be transmitted to FDA under the Biologics Industry Code (BIO) and therefore should be reviewed in accordance with the CBER Regulated Biological and Drug Products Job Aid. Licensed devices have an approved BLA, and therefore the Affirmations AofC codes STN and BLN will apply (21CFR 1.78 (c)).

Clinical investigations of these products are conducted under an Investigational New Drug Application, and therefore the AofC code IND will apply to these devices at the time of import.

Investigational Devices:

Devices that qualified experts use on human subjects, to conduct investigations of their safety and effectiveness, are considered investigational devices. The affirmation and qualifier should be the Investigational Device Exemption (IDE) Number issued by FDA (CDRH/CBER) for the product identified in the FDA line (21CFR 1.78 (h)).

In the ACE/ITDS environment, all investigational devices will be submitted using the Device Industry codes. IDEs from the two Centers can be differentiated by the prefix G in the qualifier, which is specific for CDRH regulated devices. The investigational devices submitted using the Device Industry code without the G prefix in the qualifier would be routed through the CBER validation process.

IDE Affirmation of Compliance should be followed by the Investigational Device Exemption Number, or the NSR qualifier to indicate that the device is destined for non-significant risk study.

If the NSR qualifier is used with the IDE, an Institutional Review Board (IRB) affirming NSR must be provided to FDA.

Devices:

Device products, must have an approved premarket application (PMA), a cleared 510(k) or a humanitarian device exemption (HDE) (21 CFR 1.78 (i)) and should be reviewed in accordance with the CDRH Medical Device Initial Admissibility Job Aid.
See Section VI.A, references 9 and 10, for links to lists of approved and cleared device products regulated by CBER.

PM# is the Affirmation AofC Code for both PMA-approved and 510(k) cleared devices. This affirmation and the qualifier for this code should be the Device Premarket Approval Number or the Device Premarket Notification (510(k))/De-Novo Number issued by FDA/CBER for the product identified in the FDA line. Humanitarian Device Exemption (HDE) will also come under the PM# affirmation of compliance. Premarket number should always be the number that is on the listing record along with a valid prefix denoting the application type (BD, BP, BK, BH, BM, BR, K, or P)

- PM# Affirmation of Compliance followed by the 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. The prefix BP or BM is required for conducting a search in Center Views.

- PM# Affirmation of Compliance followed by the 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 prefix BK or DK is needed for conducting a search in Center Views application.

  A prefix of BR is used for Direct De Novo devices, and a prefix of BH is used for Humanitarian Device Exemptions.

  Other Affirmations of Compliance applicable to Devices include:

  For a medical device subject to registration and listing (21 CFR 1.78 (g)):

  DFE: Affirmation of compliance code applies to the Device Foreign Manufacturer Registration Number

DEV: Affirmation of compliance code applies to the Device Domestic Manufacturer Registration number.

DLS: Affirmation of compliance code applies to the Device Listing Number.

DDM: Affirmation of compliance code applies to the Device Domestic Manufacturer Registration Number.

Medical Device Component (21CFR 1.78 (j)):

CPT: The Affirmation of compliance CPT without any qualifier applies when the article being imported is a device component that requires further processing or inclusion into a finished medical device.

For additional clarification on devices, see the CDRH Device Initial Admissibility Job Aid.

2. Import Alerts

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 and, if so, refer to that import alert for instructions. Import Alerts can be found the Center Views application. When a U.S. license is revoked or suspended, CBER will contact the Division of Import Operations Management (DIOM) and request this information be shared through an ORA issued import alert.

3. Review of Admissibility Requirements

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 with a request for detention (DTR). (For approval status of imported intermediates, active pharmaceutical ingredients, bulk substances, or other biologics for further manufacturing use, see section 3.c. below.)

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, or if there are any questions, reviewers should contact CBER, OCBQ, DCM (see Part VI.B. for program contact information). If the establishment does not have an IND or IDE in effect for its investigational products, the entry reviewer should refer the line

with a request for detention (DTR)[1]. (For approval status of imported intermediates, active pharmaceutical ingredients, bulk substances, or other biologics for further manufacturing use, see section 3.c. below.)

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 3a and 3b 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.

d. Import-for-Export Products

1. The AofC code for import-for-export products is: "IFE." 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. 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. The entry reviewer should refer to the RPM, Chapter 9 , "Import for Export Subchapter" (http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074300.pdf) and IOM Sections 6.2.3.4.1-6.2.3.4.3 for handling these entries." (http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074300.pdf) for handling these entries.

2. Blood, Blood Components, Source Plasma or Source 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

[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.

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 Part VI.B. for program contact information) 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 with a request for detention (DTR). See Part Vfor charges and actions.

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 *not* be referred with a request for detention (DTR).

2. Other Samples Consigned to the CBER Sample Custodian

If samples of products are offered for entry and 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 not be referred 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 with a request for detention (DTR). See Part V for charges and actions.

4. Device Provisions Relating to Samples

Devices (including biologics regulated as devices) intended for testing in vitro 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 with a request for detention (DTR). See Part V for charges and actions.

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 CBER-Regulated Products into the United States: Clinical Laboratories and Basic Scientific Research" at

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/BiologicsImportingExporting/ucm390716.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 6.2.3.6.1 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. For example, a shipment of 1 to 30 tubes containing 10 ml of plasma, serum, or blood would be considered samples for clinical testing. Import Divisions 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 Import Division or entry reviewer suspects diversion, they should contact CBER, OCBQ, DCM (see Part VI.B. for program contact information).

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).

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 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.

To qualify as short supply products, these products must be for further manufacture only and not for final distribution.

[2] See Ref. 11 for further discussion of routine or regular basis.

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 between a plasma broker or broker(s) and the manufacturer of a final, 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 with a request for detention (DTR). See Part V for charges and actions.

i. Recovered Plasma, Plasma, and Serum Not The Subject of a Short Supply Agreement and Intended for Further Manufacture into a Device

Recovered plasma, plasma, and serum that are not the subject of a short supply agreement and are intended for further manufacture into a device, are considered device components, and are processed under the Medical Device Industry Codes and the Center for Devices and Radiological Health (CDRH) import processes. Examples include serum or plasma intended for further manufacture into in-vitro diagnostic reagents such as clinical chemistry controls. The immediate container should be properly labeled as described in the labeling regulations (see 21 CFR 606.121 and 610.40).

If there is a question concerning the device components in the entry, labeling may be examined for:

- The name of the product (21 CFR 1.78 (a));
- Name(s), address(es), and registration number(s) of establishment(s) [21CFR 1.72(b)] collecting, preparing, labeling, or pooling the source material [21 CFR 606.121(c)(2)];
- Intended use and appropriate caution statements (21 CFR 1.72 (a)(3)):
  - Statement "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 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)(4)(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)(4)(iii)]

If the product is inappropriately labeled, the entry reviewer should refer the line with a request for detention (DTR). See Part V for charges and actions.

Other U.S. Government 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 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 Import Division 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 U.S. government 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 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 640.74(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, including biological 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 Part VI.B. for program contact information) 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 (also referred to as U.S. Goods Returned)

   American Goods Returned (AGR), also referred to as U.S. Goods Returned (USGR), is a term used for the formal declaration of goods manufactured in the United States that have been previously exported and are now being returned. If a product offered for import has been returned, rejected, or has a complaint file, the Import Division should carefully review that entry to determine the reason for the return, rejection, or complaint. In addition, products that are identified as ARG 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 may be imported by the U.S. manufacturer. In accordance with the Supplemental Guide, Intended Use Code 920.000 for return to the United States (US Goods Returned) should be submitted, and there is no requirement for an AofC.

   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 Part VI.B. for program contact information).

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. Import Divisions should use discretion in detaining a product offered for import if its use is required for a medical emergency.

   Import entries coming under this provision may be submitted using IUC 940.000 (Compassionate Use/Emergency Device) or 140.000 ((for Improving living conditions during a natural disaster).

4. Influenza Virus Vaccine Entries for the Annual Strain Changes

   For Influenza Virus Vaccine imported in advance of approval of BLA supplements for the annual strain changes, the vaccine manufacturer should submit a request to CBER identifying the product, quantities, storage conditions, and other relevant information. CBER will advise the Division of Import Operations Management (DIOM), and the manufacturer, once the import request has been deemed acceptable and the submitted reconditioning plan (Form FDA 766) for the entry has been accepted. This allows a firm to import and recondition the bulk influenza strains while held under bond.

   The applicable Import Division will notify the importer of the acceptance of the reconditioning plan. Once the BLA supplement is approved, the entries may be released.

   Questions on the process for importing Influenza Virus Vaccine shipments should be directed to: ORADIOVaccineTeam@fda.hhs.gov

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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, When sample collection is necessary, CBER will notify the Office of Regulatory Science, Office of Medical Products, Tobacco, and Specialty Laboratory Operations/ORA.

If samples are to be evaluated by CBER, contact the CBER Sample Custodian (240-402-9156) before shipping any samples. No one is available to receive samples over the weekend. Samples evaluated by CBER should generally be shipped to:

CBER Sample Custodian/FDA (FEI: 1000385447)
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

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

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PART V - REGULATORY/ADMINISTRATIVE STRATEGY

A. CHARGES[3]

1. Approved/Licensed/Cleared and Investigational Products regulated by CBER

   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 enforced by FDA. 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:

   - The article is subject to refusal of admission under section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) because it appears to be a biological product for which a biologics license is not in effect under the Public Health Service Act, Part F, Subpart 1-Biological Products, Section 351(a), and it is not the subject of an Investigational New Drug application that is in effect. Therefore, it appears to be a new drug under 201(p) of the FD&C Act that it is in violation of section 505(a) of the FD&C Act because it lacks a new drug approval and because it is

[3] 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.

misbranded under section 502(f)(1) of the FD&C Act because it fails to bear adequate directions for use [IMPORT DETENTION VIOLATION CODE = NO LICENSE]

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

- The article appears to be a new drug without an approved new drug application. [IMPORT DETENTION VIOLATION 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) in that the device appears to be a Class III device and does not appear to have in effect an approved application for premarket approval pursuant to Section 515 of the Act, or an exemption pursuant to Section 520(g)(1) [Adulteration, Section 501(f)(1)(B)]. [IMPORT DETENTION VIOLATION CODE = NO PMA]
- The article appears to be a class III device without an approved application for premarket approval, and/or a notice of completion of product development protocol filed per section 515(b) or exempt per section 520(g)(1).).) of the Act.). [Adulteration, Section 501(f)(1)(A)], [IMPORT DETENTION VIOLATION CODE=NO PMA/PDP]

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

- The labeling for this article appears to be false or misleading. [IMPORT DETETION VIOLATION CODE = FALSE]
- The article appears to lack adequate directions for use. [IMPORT DETENTION VIOLATION CODE = DIRECTIONS]

2. Import-for-Export Products

Detain all products identified as import-for-export if they do not comply with sections 801(d)(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:

- The article is subject to refusal of admission under section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) because it appears to be a biological product for which a biologics license is not in effect under the Public Health Service Act, Part F, Subpart 1-Biological Products, Section 351(a), and it is not the subject of an Investigational New Drug application that is in effect. Therefore, it appears to be a new drug under 201(p) of the FD&C Act that it is in violation of section 505(a) of the FD&C Act because it lacks a new drug approval and it is misbranded under section 502(f)(1) of the FD&C Act because it fails to bear adequate directions for use [IMPORT DETENTION VIOLATION CODE = NO LICENSE].

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

- The article appears to be a new drug without an approved new drug application. [IMPORT DETENTION VIOLATION 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) in that the device appears to be a Class III device and does not appear to have in effect an approved application for premarket approval pursuant to Section 515 of the Act, or an exemption pursuant to Section 520(g)(1) [Adulteration, Section 501(f)(1)(A)]. [IMPORT DETENTION VIOLATION CODE = NO PMA]
- The article appears to be a class III device without an approved application for premarket approval, and/or a notice of completion of product development protocol filed per section 515(b) or exempt per section 520(g)(1).).) of the Act.). [Adulteration, Section 501(f)(1)(A)], [IMPORT DETENTION VIOLATION CODE=NO PMA/PDP]

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

- The labeling for this article appears to be false or misleading. [IMPORT DETETION VIOLATION CODE = FALSE]
- The article appears to lack adequate directions for use. [IMPORT DETENTION VIOLATION CODE = DIRECTIONS]

3. Samples of Drugs, Devices and Biological Products

This section does not apply to Import of Product Samples for Lot Release, Other Samples Consigned to the CBER Sample Custodian, or to Biological Specimens for Clinical Testing or for Basic Scientific Research.

Only detain entries misidentified as samples that appear to be Drugs, Devices or Biological products.

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

- "The article is subject to refusal of admission under section 801(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) because it appears to be a biological product for which a biologics license is not in effect under the Public Health Service Act, Part F, Subpart 1-Biological Products, Section 351(a), and it is not the subject of an Investigational New Drug application that is in effect. Therefore, it appears to be a new drug under 201(p) of the FD&C Act that it is in violation of section 505(a) of the FD&C Act because it lacks a new drug approval and it is misbranded under section 502(f)(1) of the FD&C Act because it fails to bear adequate directions for use [IMPORT DETENTION VIOLATION CODE = NO LICENSE].

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

- The article appears to be a new drug without an approved new drug application. [IMPORT DETENTION VIOLATION CODE = UNAPPROVED]

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

- The labeling for this article appears to be false or misleading. [IMPORT DETETION VIOLATION CODE = FALSE]
- The article appears to lack adequate directions for use. [IMPORT DETENTION VIOLATION 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.5. below.

Products, including blood and blood components, intended for further manufacture into licensed biological products must be labeled "Caution: For Manufacturing Use Only." Recovered Plasma for further manufacture must be labeled, as applicable, "Caution: For Manufacturing Use Only" or "Caution: For Use in Manufacturing Noninjectable Products Only, " or "Not for Use in Products Subject to Licensure Under Section 351 of the Public Health Service Act." (see 21 CFR 606.121(c)(10) and 606.121(e)(4)(ii))

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

- The labeling for this article appears to be false or misleading. [IMPORT DETETION VIOLATION CODE = FALSE].
- The article appears to lack adequate directions for use [IMPORT DETENTION VIOLATION CODE = DIRECTIONS].

5. Recovered Plasma, Plasma and Serum Not The Subject of a Short Supply Agreement and Intended for Further Manufacture into unlicensed device products

Recovered plasma, plasma and serum, that are not subject to a short supply agreement, and are intended for further manufacture into device, are considered device components and are processed under the Medical Device Industry Codes and the Center for Device and Radiological Health (CDRH) import processes. The immediate container should be labeled in accordance with the applicable labeling requirements in 21 CFR 606.121 and 21 CFR 610.40.

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

- The labeling for this article appears to be false or misleading. [IMPORT DETETION VIOLATION CODE = FALSE]
- The article appears to lack adequate directions for use. [IMPORT DETENTION VIOLATION CODE = DIRECTIONS]

B. ACTIONS

For violative imported CBER regulated products that are still in import status, the enforcement options available include:

Detention	Detention of biological products, drugs, and devices based on the appearance of violations as described in section 801(a) of the FD&C Act.
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.
Administrative Destruction	Refused drugs valued at $2500 or less where FDA makes a determination of a violation, may be destroyed by FDA without opportunity for re-export.
DWPE –Import Alert	Any FDA unit may recommend DWPE (or recommend additions to existing import alerts) whenever there is information that would cause future shipments of biological products, drugs, or devices offered for entry to appear violative under laws administered by FDA. See RPM Chapter 9, “Detention Without Physical Examination” Subchapter, regarding procedures for DWPE. Recommendations for DWPE should be submitted in writing with supporting information to the Division of Import Operations Management.
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. Import Divisions should work closely with the responsible CBP office. See IOM 6.2.7.11, “Bond Action” and RPM Chapter 9 “Bond Actions” Subchapter.
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.

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PART VI - REFERENCES/PROGRAM CONTACTS

A. References

1. Investigations Operations Manual (IOM), Chapter 6 - Imports
2. Import Alerts Listing
3. Regulatory Procedures Manual, Chapter 9 - Import Operations/Actions
4. Compliance Policy Guidance Manual, Chapter 2 – Biologics
5. Lists of Licensed Products and Establishments, and approved in vitro diagnostic test kits
6. Alphabetical List of Licensed Establishments including Product Approval Dates
7. Alphabetical List of Licensed Products
8. Complete List of Donor Screening Assays for Infectious Agents and HIV Diagnostic Assays
9. Complete List of Currently Approved Premarket Approvals (PMAs)
10. Complete List of substantially equivalent 510(k) Device Applications
11. Memo to All Registered Blood Establishments, Dated February 12, 1990, Subject: Autologous Blood Collection and Processing Procedures

B. Program Contacts

CBER/OCBQ/DCM at CBERImportInquiry@fda.hhs.gov Maria Anderson: (240) 402-8883 Robert Sausville: (240) 402-9076	ORA/ OEIO Phone: (301) 796-5270 Fax: (301) 827-3670 Division of Import Operations Management Samuel Chan (301) 796-2283 Jeffrey Hilgendorf (313) 393-2019 Division of Systems Solutions, Import Systems Branch (DSS, ISB) ORAOISMDSSIMPCOMPLSYSBR@fda.hhs.gov

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PART VII - CENTER RESPONSIBILITY/PROGRAM EVALUATION

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

The ORA Imports 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 CBER should be contacted for further instructions.

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 Operational and Administrative System for Import Support (OASIS), On-Line Reporting Analysis and Decision Support System (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.

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Attachment A: Explanation of Terms Used in This Program

Autologous Blood – Autologous blood is blood collected from an individual and intended for reinfusion to the same individual.

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) - 21 CFR 312.40(a) An investigational new drug may be used in a clinical investigation if the following conditions are met:

> (1) The sponsor of the investigation submits an IND for the drug to FDA; the IND is in effect under paragraph (b) of this section; and the sponsor complies with all applicable requirements in this part and parts 50 and 56 with respect to the conduct of the clinical investigations; and

(2) Each participating investigator conducts his or her investigation in compliance with the requirements of this part and parts 50 and 56.

In Vitro Diagnostic products (IVDs)(21 CFR 809.3(a)) - *In vitro diagnostic products* are those 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. Such products 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 Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service 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)) - *Manufacturer* means any legal person or entity engaged in the manufacture of a product subject to license under the act; "Manufacturer" also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

New Drug Application (NDA) - *New drug application, or NDA* is the application described under 314.50, including all amendments and supplements to the application. An NDA refers to "stand-alone" applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and to 505(b)(2) applications.

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 - Recovered Plasma is derived from single units of Whole Blood, or Plasma, or as a by-product in the preparation of blood components from whole blood collection. It is an unlicensed raw material intended for use in the manufacture of both licensed and unlicensed products, such as licensed fractionation products for injection, licensed diagnostic products; and diagnostic products not subject to license, including clinical chemistry controls. A license is not required to manufacture, distribute, relabel, pool, or repack Recovered Plasma.

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 - Source Leukocytes is defined as human leukocytes (white blood cells) prepared manually from Whole Blood or collected by apheresis and intended as source material for further manufacturing use.

Source Plasma (21 CFR 640.60) - Source Plasma is defined as the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use. The definition excludes single donor plasma products intended for intravenous use.