FDA IMPORT REQUIREMENTS AND BEST PRACTICES FOR DRUGS AND MEDICAL DEVICES

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FDA Import Requirements and Best Practices for Drugs and Medical Devices

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1a. Introduction

A cross-functional team from branded and generic pharmaceutical and medical device companies prepared this manual in order to assist the U.S. importer of FDA regulated merchandise. Compliance to the FDA's import regulations and processes continues to be a core competency for U.S. importers as supply chains expand and become more complex. This manual should be utilized as one of many tools in an importer's tool box for compliance with U.S. Participating Government Agencies with import jurisdiction.

This manual serves as a reference source and not meant to provide any legal or regulatory advice. Please note that the abbreviation FD&C Act refers to the Food, Drug & Cosmetic Act.

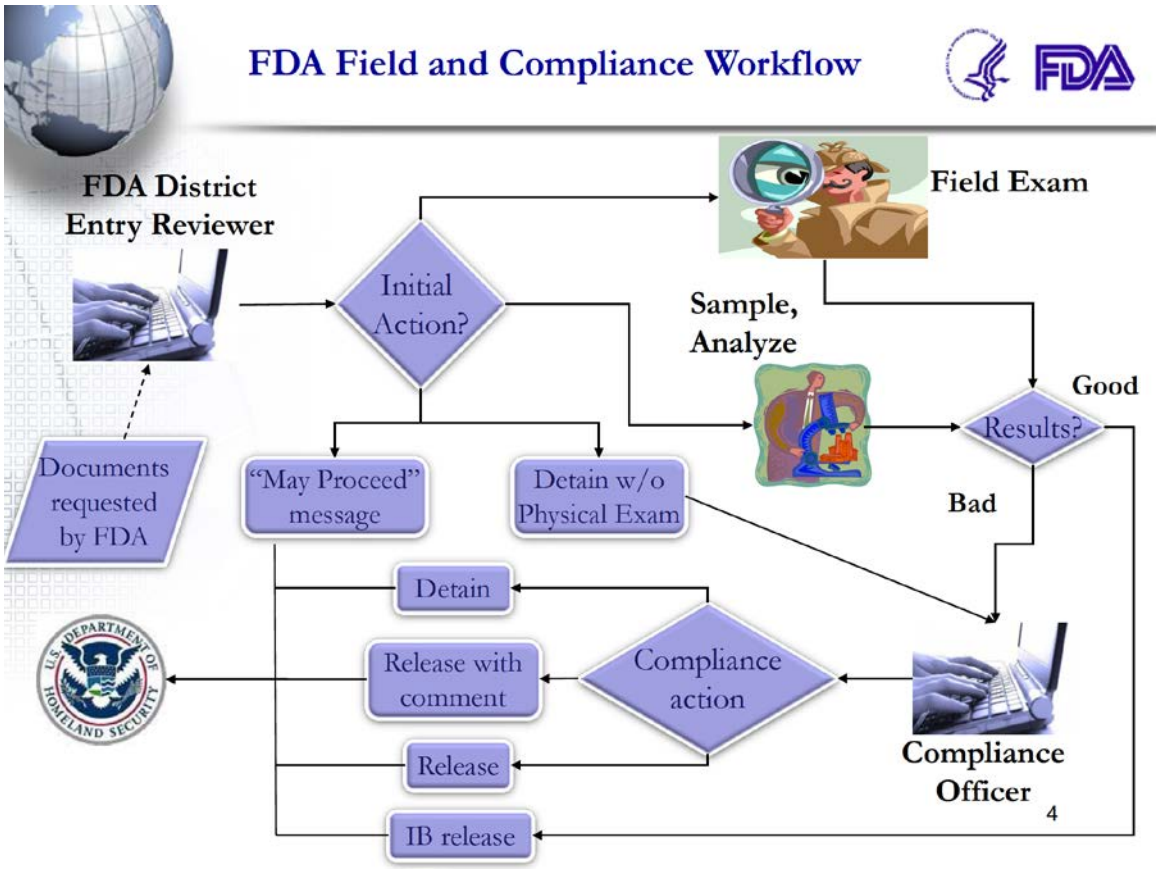
1b. Abbreviation table

ABI	Automated Broker Interface (with CBP)
ACE	Automated Commercial Environment
ACC	Accession Number
ACS	Automated Commercial System (CBP)
AofC	Affirmation of Compliance codes (for FDA)
ANC	Annual Report Accession Number
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CBP	Customs & Border Protection
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CM	Contract Manufacturer
CMC	Chemical Manufacturing Control
CPT	Component of Device
DEV	Foreign Manufacturer Registration Number
DII	Initial Importer Registration Number
DIOP	Division of Import Operations and Policy (FDA)
DLS	Drug Listing number

DUNS	Data Universal Numbering System; Dun and Bradstreet
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, & Cosmetic Act (FDA)
FEI	Facility Establishment Identifier number (FDA)
FP	Finished Product
FTZ	Foreign Trade Zone (US CBP Regulated)
HDE	Humanitarian Device Exemption
HPUS	Homeopathic Pharmacopoeia of the United States
IDE	Investigational Device Exemption
IFE	Import For Export (FDA)
IND	Investigational New Drug
ISO	International Standards Organization
ITACS	Import Trade Auxiliary Communications System
LST	Device Listing Number
MARCS	Mission Accomplishment and Regulatory Compliance Services
MID	Manufacturer Identification code
NDA	New Drug Application
NDC	National Drug Code
NF	National Formulary
OASIS	Operational and Administrative System for Import Support (FDA)
ORA	Office of Regulatory Affairs (FDA)
OTC	Over The Counter
PDP	Product Development Protocol number
PLAIR	Pre-Launch Activities Importation Request
PLD	Private Label Distributor
PMA	Premarket Approval number
PMN	Premarket Notification number

PN	Prior Notice (FDA)
PREDICT	Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting tool
REG	Drug Facility Registration Number
SPL	Structured Product Labeling
TPM	Third Party Manufacturer
USDA	United States Department of Agriculture
USHTS	United States Harmonized Tariff Schedule
USP	United States Pharmacopoeia
XML	Extensible Markup Language

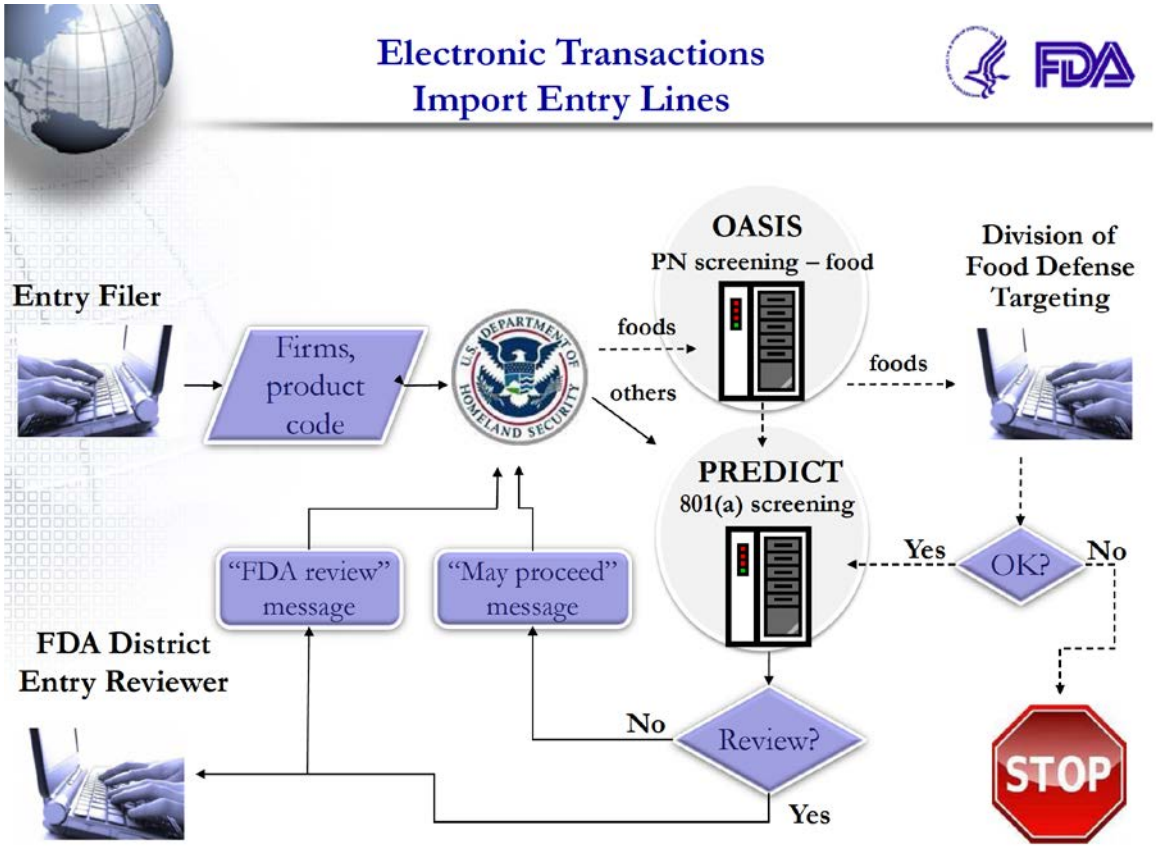
2. Importation Process Diagram



3. PREDICT

PREDICT is the FDA's **P**redictive **R**isk-based **E**valuation for **D**ynamic **I**mport **C**ompliance **T**argeting tool; which is integrated within the MARCS entry review system. Its intent is to prevent the entry of adulterated, misbranded, or otherwise violative goods while expediting the entry of compliant goods.

PREDICT will improve FDA enforcement targeting by scoring each entry line on the basis of multiple factors, increasing the number of "May Proceeds" that are issued for lower risk line items (more compliant) , and providing reviewers with line scores and the rationale behind the scores for those items assigned further review. PREDICT shifts the focus of FDA reviews from "entries" to "line items". This is accomplished by using automated data mining and pattern discoveries to develop rules in conjunction with open-source intelligence. PREDICT will query databases for relevant information such as facility registrations, drug listings, market approvals, etc. Source data may include field exams, sample analyses, results of foreign and domestic facility inspections, product code and facility code accuracy, data anomalies in transmitted information, and admissibility history (importer, exporter, manufacturer and ultimate consignee). Importers should be aware that providing consistent and accurate information (e.g. FDA Product Codes, AofCs, and FDA Manufacturer Identification code) will expedite PREDICT's line item screening.



4. MARCS

MARCS manages the integration, reengineering and enhancement of several legacy systems to better support FDA's mission.

MARCS Imports Entry Review is a web-based application for conducting entry review that includes the following enhancements:

A. Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT) screening module;

B. Integration with Import Trade Auxiliary Communications Service (ITACS);
C. Entry and line level access to a menu of pre-defined reports that provide information on past import examination results;
D. Enhanced User Preferences.

The entry reviewer will either provide a “May Proceed”, request additional information, or forward to a Compliance Officer. The Compliance Officer may resolve the entry with requesting additional information, granting a “May Proceed”, requesting a field exam, or refusing the shipment.

Field work and detention requests are processed through the MARCS system. Once the entry lines are set up for field work or the detention request has been processed the entry lines are then populated in OASIS to be assigned.

4a. MARCS Data Transmission Requirements

- **Required Data Elements:**

Five specific data elements **(A-E)** must be transmitted for FDA admissibility: Examples given below are from the FDA Product Code Builder Tutorial.

A) Commercial Description: The commercial description is an actual description of the product, usually obtained from the invoice. Therefore, the invoice must have a correct description; i.e., Trade name, Generic name, Potency, Dosage Form and Packaging Configuration.

B) FDA Manufacturer: The FDA manufacturer is the physical location at which the product is manufactured or produced. The name and address of a corporate headquarters or intermediate supplier is not acceptable. U.S. Customs and Border Protection (CBP) requires declaration of the "invoicing firm," which may not be the manufacturer. For example:

- ABC Co, in Hong Kong manufacturers a finished drug product under contract for XYZ Corp. in Peoples Republic of China.
- XYZ Corp. invoices and ships the product to the U.S.
- RESULT: FDA considers ABC Co. to be the manufacturer; CBP considers XYZ Corp. to be the manufacturer.

If the same item is produced by multiple manufacturers, each manufacturer must be shown as a separate line item by quantity and the FDA elements for each must be submitted. Reference the Appendix for the FDA Manufacturer Identification (MID) code construction. Another facility requirement is the facility annual registration with the FDA (called FEI or CFN).

C) FDA Shipper: The FDA shipper is the actual shipper of the product being imported. The FDA shipper is often identical to the invoicing party reported to CBP. Human drugs, medical devices, and biologics must always show evidence of being produced in a FDA registered facility. (Facility Establishment Identifier number (FEI).

Only if a product being imported is not subject to registration, listing or licensing and the FDA Manufacturer information is not available (after the importer has made a good-faith effort to obtain the information), may the FDA Shipper information be transmitted in lieu of the FDA Manufacturer information. In this case, the FDA country of origin remains the country of the site-specific manufacturer. Reference the Appendix for the FDA Manufacturer Identification (MID) code construction.

D) FDA Country of Origin**:** The FDA Country of Origin is needed for electronic screening. FDA considers the country of origin to be that of the actual manufacturer of the final drug product. CBP considers the country of origin to be the last location of substantial transformation. Most of the time the last location of substantial transformation is the API manufacturing location. For example:

- ABC Co. in Japan manufactures an API, which is used in the manufacture of tablets by XYZ Corp. in Korea.
- FDA regulates both the API and drug product, but considers the country of origin to be Korea, where the tablets were manufactured.
- CBP considers Japan to be the country of origin because this is the last location of substantial transformation .

When 2 or more active ingredients are combined in manufacturing, FDA and CBP both typically consider the country of origin to be that of the actual manufacturer of the final drug product.

Suggestion: For assistance with CBPs country of origin determination, contact your internal Trade Compliance, Legal department, consulting firm or Customs representative.

E) FDA Product Code: A FDA Product Code is "built" from the FDA product code builder found on the web (http://www.accessdata.fda.gov/scripts/ora/pcb/pcb.htm). It is a 7 character, alpha-numeric code that indicates, among other things, the action of the drug, the active ingredients, the final dosage form, human/animal/investigational use, and prescription requirements. Reference the Appendix for the FDA Product Code builder.

Optional Data Elements:

Optional information may be declared in OASIS, when applicable. Providing additional FDA data will help expedite the review process. Examples of four **(A-D)** optional data elements are below.

Affirmation of Compliance Codes (AofC): The AofCs help the FDA evaluate the import by further defining the import. The FDA validates the AofCs provided against various FDA databases. If accurate A of C's are provided the entry may pass the new system auto look-up and may be "May Proceeded" by the system. If the entry does not pass auto look-up then it will be manually reviewed by an Entry Reviewer. If the A of C information has been supplied, the entry reviewer may be able to release the entry during their initial review. If A of C codes are not provided, the entry will not pass auto-look, and will require documents to be submitted for review by an Entry Reviewer.

A of C Codes to provide for drugs:

- Regulatory Filing Number (NDA, ANDA, BLA, IND, etc.)
- DLS (Foreign Drug Listing #)
- NDC (U.S. Drug Listing #)
- Drug Facility Registration Number (REG)

A of C Codes to provide for devices:

- Foreign Manufacturer Registration Number (DEV)
- Device Listing Number (LST)
- Foreign Shipper Registration Number (DFE)
- Initial Importer Registration Number (DII)
- Premarket Notification Number or 510K (PMN) - for Class II Devices only
- Premarket Approval Number (PMA) – for Class III Devices only

A of C Codes to provide for device components:

- Component of Device (CPT)
- Device Listing Number (LST) and Initial Importer Registration Number (DII) of the finished device
- FDA Product Code of finished device

A of C Codes to provide for Radiological Health Devices:

- Accession number (ACC)
- Annual Report Accession number (ANC)
- Model Number (MDL)
- Component (CPT)

(See Appendix E, Useful Links, page 41)

Each product's HTSUS code and FDA Product Code will indicate the need for registration and listing. When the HTS code for a product which may be under FDA jurisdiction is submitted to CBP, it directly triggers one of the following FDA "flags" in ACS: FD0, FD1, FD2, FD3 and FD4. The flag provides an indication of whether products are or may be under FDA jurisdiction, whether prior notice or other entry information is required, and the basis to "Disclaim" a product from FDA notification requirements.

FD0 - Indicates that FDA has determined the article, even though subject to FDA's laws and regulations, is acceptable for CBP release without further presentation of prior notice or other entry information to FDA.

FD1 - Indicates that the article may or may not be subject to FDA jurisdiction, including FDA review under 801(a) of the FD&C Act. For products not subject to FDA jurisdiction based on their intended end use, a filer can "Disclaim" the product from FDA notification requirements. The FDA will periodically review "Disclaimed" entries to confirm the accuracy of the declaration.

FD2 - Indicates that the article is under FDA jurisdiction and review of entry information by FDA under section 801(a) will take place. However, the article is not "food" for which prior notice information is required.

FD3 - Indicates that the article may be subject to prior notice under section 801(m) of the FD&C Act and 21 CFR Part1, subpart I. , e.g., the article has both food and non-food uses.

FD4 - Indicates that the article is "food" for which prior notice is required under section 801(m) of the FD&C Act and 21 CFR Part1, subpart I.

Exceptions to registration and listing include:

- Inactive ingredients and excipients
- Intermediates (non-API)
- Drug products not intended for importation into the United States (Foreign Trade Zone, FTZ)
- Drugs imported under an Investigational New Drug (IND) Application (21 C.F.R. 312)
- Components of drugs imported under 801(d)(3), Import for Export (IFE).

Quantity: Quantity data provides additional information to FDA about the product and how it is packaged. The basic format for Quantity Data is in multiple pairs of data – quantity and unit of measure, i.e., 500 cases, 12 ounces, fluid, 1000 cartons, etc. Up to 6 data pairs may be submitted. The first pairs describe the containers. The last pair must describe the amount of product in the smallest container. Here are some examples:

Product: 1000 cases of mineral water, 24/12 ounce bottles in each case
Data pairs: 1000 CS (Case)
24 BO (Bottle, Non-protected, Cyl)
12 FOZ (Ounces, fluid)

Product: 200 cartons of 100 rolls surgical gauze, 75 square yards per roll
Data pairs: 200 CT (Carton)
100 RO (Roll)
75 SYD (Square Yards)

Product: 100 cartons of 24 aspirin bottles, 100 tablets, 325 mg.
Data pairs: 100 CT (Carton)
24 BO (Bottles, Non-protected, Cyl)
100 TAB (Tablets)

Quantity for bulk drug product examples:

Product: 10 drums of 15kg API (All drums are the same Kg weight)
10 DR

15KG

Product: 10 drums of 15kg API and a drum of 5kg (drums of various weights)
155kg; or,
Transmit 2 lines:

1) The first line quantity:
   10dr
   15kg
2) The second line quantity
   5kg

http://www.accessdata.fda.gov/scripts/ora/pcb/tutorial/information.pdf

Value**:** The value must be declared in U.S. dollars. The value of the FDA line cannot exceed the value of the Customs entry. To ensure the Customs line/entry value is not exceeded, it is permissible to decrease the FDA line value. Line value adjustments should be recorded on the invoice. These annotations will expedite review and comparison of the entry documents to the electronic data.

Consignee: The FDA consignee data field is transmitted only when the Customs consignee is not a U.S. firm.

4b. FDA Establishment Registration

As of June, 2009, all new facility registrations (FEI), drug listings (DLS), and labeler codes are required to be registered electronically (eDLS). They must be submitted in XML format through the FDA gateway. http://www.accessdata.fda.gov/scripts/cder/drls/default.cfm

The submission populates FDA internal and external databases immediately after having passed FDA validation criteria. It is closely linked to application filings and increases the amount of detail about the supply chain that is provided by the application holder and marketer.

Annually, each foreign manufacturing facility must be registered electronically by its U.S. Agent. Registration requires a DUNS number (issued by Dun and Bradstreet), and FDA's FEI number US Agent, and importer information. For the purposes of electronic registration, FDA considers importers to include the ultimate consignee, or physical recipient, of the product, not just the importer of record.

Any importer responsible for import of a drug or device must ensure their facility is listed under the foreign manufacturer's site establishment registration. The following information must be submitted electronically to the FDA by the foreign establishment to support applicable importer information:

Importer Name, DUNS, Telephone number and Email address for Importer Contact

5. OASIS

OASIS is the **O**perational and **A**dministrative **S**ystem for **I**mport **S**upport. This automated FDA system is the legacy system that has been integrated into the web based MARCS system. Customs brokers are electronically routed to the OASIS system through the Automated Broker Interface (ABI) software with U.S. Customs when a FDA declaration is required by the U.S. Harmonized Tariff System (USHTS) code declared or by the import's usage in FDA regulated merchandise. OASIS communicates electronic admissibility decisions to customs brokers through ABI.

OASIS is the system used to record field work conducted, and entry lines sent to Compliance for further review.

6. Import Trade Auxiliary Communications System (ITACS)

The ITACS internet portal is an optional FDA system which allows the trade community to check the status of individual entries/lines, electronically submit entry documentation to FDA and provide shipment examination availability/location information to the FDA.

Note: Entry documentation can include applicable Customs forms, bills of lading, commercial invoice, end use letter, certificates of analysis, IFE chain of custody letter, and whatever else is appropriate for the import package. FDA would like to limit ITACS submissions to only entry documents.

Filers and importers are able to search using the Customs entry number, with Customs or FDA line numbers as optional inputs. An individual account is not required with the current functionality of the system.

Possible future functionality includes transmission of Notice of FDA Action (accounts will be required for this functionality), queries for FDA firm identifiers and product codes, submission of additional document types, display of laboratory timeframes and link to FDA import reference materials.

Examples of ITACS Statuses:

1) Submit Entry Documents to FDA (Invoice, Bill of Lading, CBP Entry Document)
2) Line Availability Received, FDA Examination Pending
3) Notify FDA of Location for FDA Examination
4) Detained – Refer to Notice of FDA Action for Violation Charges
5) Entry closed by FDA

Examples of ITACS statuses without clear definition:

1) **No public status available**: indicates the current step in the FDA admissibility review does not have a correlated status.
2) **Entry status information not available pending receipt of Conveyance Arrival Notification:** indicates it appears the entry has not been arrived by or transacted to Customs by the carrier. This can be done via the broker.

To expedite entry review of R&D shipments, it is recommended that the filer upload the documents via ITACS at the time the entry is submitted. By uploading the documents before they are requested, the entry may be released upon the initial review by the entry reviewer. If the documents are not uploaded in advance, then the entry reviewer will conduct the initial review, and then ask for the entry documents. The documents should include an *Intended Use Letter*. The entry will be reviewed again once the documents are received.
Note: Some ports ask that we not submit in advance.
ITACS link: https://itacs.fda.gov

7. Drug Importation

7a. What is a drug?

According to FD&C Act 201(g)(1), a drug is “intended to diagnose, cure, mitigate, treat or prevent disease in man or other animals…it is intended to affect the structure or any function of the body of man or other animals (other than food)…it is recognized in the USP/NF, HPUS (Homeopathic) or their supplements…or is intended for use as a component of a drug.”

A “new” drug FD&C Act 201(p) is defined as any drug the composition of which…is not generally recognized among experts qualified by scientific training and experience as being safe and effective (GRAS/E) for use under the conditions prescribed, recommended or suggested in the labeling. New drugs must be covered by an approved New Drug Application in order to be marketed in the U.S. or under an Investigational New Drug application (IND). This definition applies to both prescription and over-the-counter (OTC) medications.

Prescription drugs cannot be used safely without a doctor's supervision and require a prescription. Those medicines that can be used safely without medical supervision are considered over-the-counter drugs (e.g. aspirin or acetaminophen). If a drug can be marketed as over-the-counter, it must be marketed as over-the-counter.

Under the Food Drug and Cosmetic Act, a chemical may be considered a drug, but not all chemicals are drugs. Some cosmetics may also be drugs (e.g. a cosmetic that offers anti-aging claims, anti-microbial soap or antiperspirant/deodorant). In these cases, the products must meet the requirements for both cosmetics and drugs.

7b. What is an unapproved drug?

Unapproved new drugs are any drugs, including foreign-made versions of U.S. approved drugs, which have not been manufactured in accordance with and pursuant to a FDA approval. Absent evidence that the specific drugs sought to be imported from a foreign country have been manufactured pursuant to an approved new drug application, in the manufacturing facility permitted under the application, such drugs would appear to be unapproved new drugs subject to FDA enforcement action.

7c. Drug Development & Steps Toward Drug Approval

When determining sourcing strategies for drugs, it is helpful to have a general understanding of the FDA drug approval process. Importation of unapproved drug into the U.S., unless the material is exempted through one of the intended uses specified in the C.F.R., (labeling exemption 21 C.F.R. 201.122a, b, c) is prohibited. Importers must document to the FDA, the intended use of unapproved drugs, and must label the drug appropriately.

There are several steps necessary to obtain drug approval:

Discovery Phase

- Work to demonstrate biological activity of a discovery compound
- Understand the therapeutic potential
- Investigate if the compound is marketable
- Select a lead compound to further develop

Preclinical Development

- Study the pharmacokinetics of the drug
- Conduct formulation work of a finished dosage form
- Development GMP manufacturing processes
- Conduct toxicology studies
- Perform analytical work on drug for potency, stability, etc.
- Develop a clinical plan to test the drug in humans
- Author all required regulatory documents for the FDA and other Agencies
- Determine marketing strategy

Clinical Development → File the IND (Investigational New Drug Application)

- Prepare investigational supplies for various phases of the studies in humans
    - Phase I – Determine tolerance of drug in 20-80 healthy subjects for a short period of time. Frequently the drug is administered in a clinic.
    - Phase II – Determine the efficacy of the drug in approximately 50-200 patients with the disease to be studied. Usually multiple doses, and attempt to define dose to be marketed.
    - Phase III – Defines the safety and efficacy of clinical significance with a larger population of 100-2500 with the disease process in a broader population in numerous global centers.
- Continue to manufacture batches and finalize the manufacturing process.
- Develop a marketing plan.
- Continue to prepare regulatory documents.
- File the NDA (New Drug Application).
- Market the drug and support ongoing required safety monitoring.
- FDA approval and commercial distribution.

7d. Active Pharmaceutical Ingredient (API) Importation

Definition: Active Pharmaceutical Ingredient (API) – "Any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug" [21CFR207.3]

APIs imported into the U.S. are subdivided into the following five categories based on intended use:

1. Use in an approved NDA, ANDA or supplement (21C.F.R. 201.122(a))
2. Use in a pre-submission or pending NDA, ANDA or supplement (21 C.F.R. 201.122(c))
3. Use in pharmacy compounding (21 CFR 201.120)
4. Use in prescription drugs not currently subject to application requirements
5. Use in drugs for teaching, law enforcement, research & analysis (21C.F.R. 201.125)

For API intended for use in approved NDA, ANDA or supplement, the following requirements apply:

- Establishment Registration and Drug Listing of the NDC number for the API and finished dosage form (see section pertaining to Facility Establishment and Drug Listing)
- API is manufactured by the supplier approved in the new drug application
- Prescription (Rx only) and over-the-counter (OTC) drugs are covered by an approved application
- API container labeling must include the following statements to satisfy the exemption to the Adequate Directions for Use (FD&C Act 502(f)(1) & 21 C.F.R. 201.5):
    - "Caution: For manufacturing, processing, or repacking"
    - "Rx only" when *most* dosage forms in which the API may be used are subject to a prescription
- Other recommended information in shipment documentation and/or container labeling:
    - API product name and NDC number of the API (drug substance)
    - Name and address of API manufacturer
    - Number of the approved NDA/ANDA or supplement
        - Note: For imports of finished drug product or API that is subject to a supplemental filing (e.g. CBE-30), it is recommended to provide a copy of the cover letter of the submission along with the End Use Letter or other correspondence.
    - Finished dosage drug product name and NDC number of drug product

For API intended for use in pre-submission batches or pending NDA, ANDA or supplement, the following requirements apply:

- API is manufactured by the supplier in the pending or in the case or pre-submission batches, the intended NDA, ANDA or supplement
- Applies to prescription (Rx only) and over-the-counter (OTC) drugs
- API container labeling must include the following statements to satisfy the exemption to the Adequate Directions for Use (FD&C Act 502(f)(1) & 21 C.F.R. 201.5):
    - "Caution: For manufacturing, processing, or repacking"
    - "Rx only" when *most* dosage forms in which the API may be used are subject to a prescription
- Other recommended information in shipment documentation and/or container labeling:
    - API product name and NDC number of the drug substance
    - Name and address of API manufacturer
    - For pre-submission batches, the name and address of consignee
    - Number of the pending NDA/ANDA or supplement
    - Finished dosage drug product name and NDC number
    - Written commitment that products manufactured with API will not be introduced in commercial distribution until approved
    - Additionally, for Pre-submission batches, a written explanation that API is intended to generate data to submit an application/supplement

Pre-submission batches are used to conduct the studies needed to generate data required for the support/approval of the application or supplement, but may be marketed upon such approval (e.g. pre-submission batches or bioequivalence or stability batches).

For API intended for use in Pharmacy Compounding, the following requirements apply:

- API container labeling must include the following:
  - "For Prescription Compounding"
  - "Rx only"
- Other recommended information:
  - API is a component of an FDA approved drug
  - API meets official compendial requirements when applicable (e.g. Certificate of Analysis)
  - Drug has not been withdrawn or removed from the U.S. market for public health reasons (list in Compliance Policy Guidance CPG 460.200 http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm)
  - API product name and NDC #
  - Written commitment that the API will be sold and used solely for pharmacy compounding by a state licensed pharmacy or federal facility
  - Written commitment that the drug has not been withdrawn or removed from the U.S. market for public health reasons

For API intended for use in Prescription Drugs not currently subject to application requirements:

- API container labeling must include the following:
  - "Caution: For manufacturing, processing, or repacking"
  - "Rx only"
- Other recommended information:
  - Name and NDC# of product to be manufactured with the API
  - API label content demonstrating compliance with (21 C.F.R. 201.122)
  - A statement (End Use Letter) justifying why an approval is not required for the finished drug product. Example:

Sample End Use Letter – Print on Company Letterhead

Include a shipment identifier such as the entry number.

> *Drug Name* is used by *Company Name* to manufacture the following grandfathered *Drug Name* products:
>
> - Drug Name, Description, NDC #
> - Drug Name, Description, NDC #
> - Drug Name, Description, NDC #
>
> These non-NDA'd products are considered by FDA to be grandfathered drugs, as these drugs were on the market prior to 1938. Following enactment of the 1938 law, drugs on the market prior to 1938 were exempted or "grandfathered", and manufacturers were not required to file a New Drug Application (NDA)[1]. For this reason, there is no supporting application documentation for these non-NDA'd *Drug Name* drug products.
>
> [1] Lewis, B. and Castle, R., Grandfathered Drugs of 1938, American Pharmacy, Vol. NS 18, No. 13, December 1978.

For API/Finished Drug Product intended use in teaching, law enforcement, research and analysis:

- Includes Rx and OTC drug products
- Shipped to persons regularly and lawfully engaged in instruction in pharmacy, chemistry or medicine not involving clinical use, or engaged in law enforcement, or research not involving clinical use, or in chemical analysis, or physical testing, and is to be used only for such purposes.
- Provide the following information:
  - Product name and NDC number
  - Name and address of the drug manufacturer
  - Name and address of U.S. Consignee
  - Written commitment that the quantity offered for import is reasonable for the contemplated research, teaching, analysis, etc.

7e. Drug Listing (DLS)

The Drug Listing Act of 1972 requires that all foreign firms that manufacture, prepare, propagate, compound, or process a drug imported or offered for import into the United States shall:

- Register the name and place of business
- Designate a U.S. Agent - provide business name, DUNS, contact email and phone number
- Provide names of each known importer (business name, DUNS, contact email and phone number)
- List of all drug products imported or offered for import into the U.S.

*See Section 510 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §360) and 21 CFR 207.

Drug Products are identified and Listed using a unique, three-segment number called the foreign manufacturer's drug listing number (Affirmation of Compliance code – DLS)*. It is recommended that the importer transmits the DLS number to the FDA for imports of API, bulk Drug products, and packaged finished dosage forms.

* This affirmation and qualifier should be the Drug Listing (DLS) Number which is issued by individual companies and sent to the FDA via the electronic portal. NOTE: The labeler code which is the first segment of the DLS number is issued by the FDA. All foreign drug establishments shall comply with the drug listing requirements.

The first segment of the DLS number is the labeler code. This number identifies the manufacturer of the product. The second segment of numbers identifies the specific ingredient/strength/formulation manufactured by the firm. The last segment of numbers identifies a specific package code. products. (eg, DLS 44444-333-22, DLS 4444-4444-22, DLS 55555-333-22, DLS 55555-4444-1)

Imports of packaged, finished dosage form drug products for commercial distribution in the US require the Application holder/distributor's drug listing which is the National Drug Code (Affirmation of Compliance Code – NDC)* in addition to the foreign manufacturer's DLS.

*This affirmation and qualifier is the National Drug Code (NDC) listed with FDA/CDER for the finished dosage form drug product. The qualifier required is the NDC number assigned to the product by FDA/CDER. (eg, NDC 4444-333-22, NDC 4444-4444-22, NDC 55555-333-22, NDC 55555-4444-1)

The information submitted as part of the Listing process (i.e. NDC) is used in the implementation and enforcement of the ACT. Currently, the FDA's NDC Directory is updated daily and drug information reported via the Structured Product Labeling (SPL) will not be updated until the next data compilation. The NDC Directory indicates the date it was last updated at the bottom of the webpage.

In May 2009, the FDA published the Final Guidance for Industry on the new electronic Drug Registration and Listing System (eDRLS) (See Appendix E, Useful Links), establishing an electronic Drug Listing process using SPL files with coded metadata fields. As of June 1, 2009, the FDA no longer accepts drug listings in paper format (Form FDA 2657). Based on recent port experience, it is suggested that all drug listings submitted prior to June 2009 in paper format be updated and resubmitted electronically, if still applicable and current, or to update drug listing with current information via the electronic submission. Electronic drug listing permits FDA to automatically populate the Agency's internal Listing databases and the NDC Directory (See Appendix E, Useful Links). In addition, most drug listings are posted on the DailyMed website and Labels.fda.gov (See Appendix E, Useful Links).

Note: June 1, 2011 changes were implemented to the NDC Directory. The scope is marketed human drug products and includes prescription, OTC, and unapproved products. The NDC Directory does not contain all Listed drugs. It does not include animal drugs, blood products, or human drugs that are not in final marketed form, such as active pharmaceutical ingredients drugs that are marketed solely as part of a kit or combination product, inner layer of a multi-level packaged product, or manufacturer's drug listings. For NDCs to be included on the NDC Directory they must be electronically drug listed.

In 2011, the FDA further clarified the electronic drug listing requirements for Private Label Distributors (PLD) and manufacturers, stating that the move to electronic listing was not providing all the necessary information regarding the supply chain of a product as originally intended. Both manufacturers and PLDs must drug list their products whether manufactured by a contract manufacturer (CM) or intracompany. Additional marketing

categories were added to the SPL data list which further defined the responsibilities for drug listing. Examples include:

Approved Drug Product Manufactured Exclusively for a Private label Distributor: This clarifies that CMs (also called Third Party Manufacturer [TPM]) who manufacture drug product exclusively for a PLD must drug list their product using their own manufacturers DLS number (see section 6e glossary below). These DLS numbers are not transmitted/posted on DailyMed, but are available in FDA's internal databases.
If the CM also markets the product under its own labeler code then a complete SPL with that Labeler and respective NDC for its own product(s) and those that it contract manufacture(s) would need to be Listed. The CM would not be required to submit two separate SPLs under this or any other marketing category.

Suggestion: Transmit the CM's DLS code for importation of the product along with the PLD's Final Drug Product NDC.

Bulk Ingredient: This category is used for API – 100% purity and must be drug listed with the foreign manufacturers' own DLS number. These DLS numbers are not transmitted/posted on DailyMed, but are available in FDA's internal databases.

Suggestion: Use the Manufacturer DLS code for importation of the product.
Note: Currently, there is no mechanism to drug list CBER regulated active ingredients. Therefore, DLS numbers are not applicable at time of import.

Drug for Further Processing: (Intermediate drug product): This category is used for drug substance mixed with inactives/excipients, but not yet in finished dosage form (i.e. granulation classified under HTSUS heading 3003). Intermediate drug products do not require drug listing by the manufacturer.
Suggestion: FDA at the port often delays Intermediate drug products and will inquire about the manufacturer's drug listing. This is typically due to the FDA needing clarification whether the import is in API, Intermediate, or finished dosage form. It is recommended that the description of the imported goods on the shipping documents and also the description transmitted to the FDA include the following "INTERMEDIATE DRUG PRODUCT FOR [*name of drug product*]".

Drug Product for Further Processing (packaging): This category is used for drug product in finished dosage form for packaging operations (i.e. bulk drug product that requires further packaging and labeling) and must be drug listed with the manufacturers DLS number. Content of labeling is not required, but a shipping label should be included in the SPLs Principal Display Panel section. These DLS numbers are not transmitted/posted on DailyMed, but are available in FDA's internal databases.

Suggestion: Use the Manufacturer DLS code for importation of the product.

Currently, inconsistencies are seen at various ports of entry with regard to the NDC numbers needed at the time of import. Both distributor (PLD) NDC and manufacturer DLS/NDC numbers are being accepted.

Drug Listing Glossary

Active Pharmaceutical Ingredient (API): "Any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug" (21 C.F.R. 207.3)

Data Universal Numbering System (DUNS): Dun & Bradstreet assigns and maintains a database of the D-U-N-S® Numbers, which serve as unique identifiers (codes) of business entities. Each business entity/location (headquarters, branch, subsidiary, establishment, importer, US Agent) is assigned a distinct site-specific 9-digit D-U-N-S® Number. The site-specific D-U-N-S® Number for an entity is a useful resource for FDA in identifying the establishment and a required part of registrations and listings.

National Drug Code (NDC): Unique, three-segment number used to identify drug product or API. The three segments of this code are divided as follows: Labeler code – Product code – Package code

- Labeler code: first segment - represents a manufacturer, including a repackager or relabeler, or, for drugs subject to private labeling arrangements, the entity under whose own label or tradename the product will be distributed. Assigned by FDA.
- Product code: middle segment – represents the specific drug product and dosage form or API. Assigned by the company.

- Package code: last segment – represents the packaging presentation (30 ct bottle, drum). Assigned by the company.

7f. Drug Labeling for Importation

Intent of use is determined by labeling, advertising matter, oral or written statements and circumstances surrounding distribution of the product. All drug labels must bear:

- The name and place of manufacturer, packer or distributor (FD&C Act 502(b); 21 C.F.R. 201.1)
- An accurate statement of the quantity of contents, understandably and in English (FD&C Act 502(b)(2); 502(c); 21 C.F.R. 201.15)
- The established name and quantity of each active ingredient (FD&C Act 502(e); 21 C.F.R. 201.10)
- The established name of each inactive ingredient in alphabetical order (FD&C Act 502(e); 21 C.F.R. 201.10)
- Adequate directions for use (unless exempt – 21 C.F.R. 201.5) (FD& C Act 502(f)(1); 21 C.F.R. 201.5)
- Warnings against unsafe use (FD&C Act 502(f)(2))
- Expiration dates (21 C.F.R. 201.17 & 211.137)
- Lot number (21 C.F.R. 201.18)
- "Rx only" for drugs for processing, repacking or manufacturing (FD&C Act 503(b)(1); 21 C.F.R. 201.122(a) & (c))
- Finished dosage form prescription drugs are exempt if they meet all conditions in 21 C.F.R. 201.100. Please reference 21 C.F.R. 201.100 for the criteria for an exemption.

Adequate directions for use: "directions under which a layman can use the drug safely and for the purposes for which it is intended". All drugs, including API must bear "adequate directions for use" or meet one of the exemptions (please see API section for details regarding adequate directions for use in API labeling):

- 21 C.F.R. 201.122(a) - API intended for use in a product approved in NDA, ANDA or supplement
- 21 C.F.R. 201.122(b) - API intended for use in a product subject to IND
- 21 C.F.R. 201.122(c) - API intended for use in a product pending/near NDA, ANDA or supplement approval
- 21 C.F.R. 201.125 – API intended for use in teaching, law enforcement, research and analysis and not for use in humans
- 21 C.F.R. 312.160 – Finished drug intended for IND use in laboratory research animals or in-vitro testing

7g. R&D Human Use/Investigational Samples

Importing Investigational New Drugs (IND) (Human Use) 21 C.F.R. 312.110

Once an IND has been filed, unapproved drug is permitted to be imported per 21 C.F.R. 312.110. Reference the specific C.F.R. Labeling Exemption that is required to import. The requirements are listed below:

- The original IND or CMC supplements must be submitted to the FDA.
- The IND number should be available to reference on the shipping documentation. Drug can be shipped as soon as the IND number is assigned by the FDA.
- The IND number should be included on all shipping documentation and invoices.
- Material should be utilized for the IND referenced in the shipment.
- Several IND's may be in referenced one shipment, and inventories are to be tracked by the receiving site, and made available if requested.

In order for active pharmaceutical ingredient (API, also called DS, drug substance) or finished product (FP, also called DP, drug product) to be imported into the U.S., CMC information for the exporting site must be included in the original IND or in a supplement to the IND. A copy of the cover letter to the FDA containing the IND number should be provided if the supplement has just recently been submitted to the FDA (less than 4 weeks). This should accompany the shipping documentation (Commerical Invoice, USDA Permit, Air waybill, etc.) needed to import the API or FP. Otherwise, the IND number needs only to be included as AofC and shipping documents.

The FDA's CDER database may not be updated to include the recent submission which is used at the U.S. Port. It is recommended to include hard copies of the documents which will facilitate the FDA Import review. If the filing or supplement is recent to the time of import, the FDA at the port may need a copy of the cover letter that was submitted to the FDA Reviewing Division along with a brief description of the CMC changes. Note: A shipment can be imported directly by a clinical investigator, if they are listed in the IND

Bulk Active Pharmaceutical Ingredient (API) and Finished Product (FP) imported under the IND for Clinical Trial Use

Once an IND has been submitted to the FDA, bulk containers of API or FP should be imported per labeling exemption 21 C.F.R. 201.122 (b) - Drug limited to investigational use. The requirements are listed below.

- The original IND must be submitted to the FDA. It is not permissible to import drug for human use prior to submission of the IND.
- Must have an IND number for this approval.
- The exporter and importer should be listed in the CMC section of the IND.
- API and/or FP should be listed in the CMC section of the IND.
- For shipping documentation and database entry AofC – IND qualifier (IND No.)
- Labeling statement must be on the product container as per 21 C.F.R. 201.122 (b): *"Caution. For manufacturing, processing, or repacking in the preparation of a new drug or new animal drug limited by Federal law to investigational use."*

Packaged Subject/Patient Supplies for IND Clinical Trial Use

Once an IND has been submitted to the FDA, packaged subject/patient supplies should be imported reference labeling exemption 21 C.F.R. 312.6 – Labeling of an investigational new drug. The requirements are listed below.

- The original IND must be submitted to the FDA.
- Must have an IND number for this approval.
- The exporter and importer should be listed in the CMC section of the IND.
- Finished product should be listed in the CMC section of the IND.
- For shipping documentation and database entry AofC – IND qualifier (IND No.)
- Labeling statement must be on the product immediate container and/or kit box as per 21 C.F.R. 312.6: *"Caution: New Drug-Limited by Federal (or United States) law to investigational use."*

7h. Research & Development (R&D) /No Human or No Commercial Use (Unapproved)

The regulations governing the importation of API and Finished Product (FP) for use in research and development and/or validation work is listed under 21 C.F.R. 312.160 – drugs for investigational use in

laboratory research animals or in vitro tests. API and FP imported for non-human use prior to filing an IND can be imported by following the steps below: Research & Development (R&D) / No Human or Commercial Use

- Include in the importer product description field “Drug Name, R&D, No Human/ No Commercial Use”.
- The labeling statement on each container should state: "Caution: a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans.”
- No FDA prior approval or notification is needed at the time of importation. There is not a requirement to file an IND, NDA, and ANDA.
- There is no AofC.
- The intended use of the material for non-human use cannot be changed to human use once imported.
- All shipping documents from the exporter should include the cautionary statement and reference C.F.R. 312.160.
- Include an End Use Letter to clarify for the FDA Reviewer the intended use of the drug. This letter must include a signature, either handwritten or certified electronically.

Sample End Use Letter - Printed on Company Letter Head – Suggested Format
FDA

Dear Sir or Madam:

AWB:

Entry #:

Date:

SUBJECT: (Give brief description of the product being imported)

This Research & Development (R&D) / No- Human or No-Commercial Use material is being imported under 21 C.F.R.312.160 which allows importation of drugs for investigational use in laboratory research animals or in vitro tests. This material will be used for investigational use in non-food producing research animals or in vitro testing only. It is NOT for use in humans and is NOT for commercial distribution. Once testing is completed, all unused material will be disposed of in a way that does not expose humans to risks from the drug, either directly or indirectly. If you have any questions please feel free to contact us.

Sincerely,

(Name and Title)

7i. Non-Human Use (Approved and Unapproved)

The regulations governing the importation of API and Finished Product (FP) for use in teaching, law enforcement, research, and analysis for non-human use (Non-Clinical/Post IND Research) is C.F.R. 201.125. The regulations state that drug may be imported for those lawfully engaged in the instruction in pharmacy, chemistry, or medicine not involving clinical use or engaged in research not involving clinical use, or in the analysis of physical testing. The following steps should be followed:

- The labeling statement on each container should state: "21 C.F.R. 201.125 Drug for use in teaching, law enforcement, research, and analysis."
- Include application number if application is approved.

- No FDA prior approval or notification is needed at the time of importation.
- Description: “Product Name. Non-Human Use, Drug for law enforcement or analysis.
- AofC.: optional NDA
- All shipping documents from the exporter should include the cautionary statement, "Drug for teaching, law enforcement, research, and analysis", and reference C.F.R. 201.125.
- Include an End Use Letter to clarify for FDA Reviewer what the intended use of the drug.

Sample End Use Letter – Print on Company Letter Head. This letter must include a signature, either handwritten or certified electronically.

FDA

Dear Sir or Madam:

AWB:

Entry #:

Date:

SUBJECT: (Give brief description of the product being imported)

This material is being imported under NDA XXXXX (optional), and the CFR labeling exemption (21 CFR 201.125) which allows for importation of drugs for use in teaching, law enforcement, research and analysis. This material will be used for research, analysis or testing and is not involving clinical use. It is NOT for use in humans and is NOT for commercial distribution. Once testing is completed, all unused material will be disposed of in a way that does not expose humans to risks from the drug, either directly or indirectly. If you have any questions please feel free to contact us.

Sincerely,

(Name and Title)

8. Devices

Medical devices imported into the United States must meet the requirements of U.S. Customs and Border Protection and the FDA. Each type of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The three classes and the requirements which apply to them are:

Device Class and Regulatory Controls

1. Class I General Controls (i.e., bandages)
    - With Exemptions
    - Without Exemptions
2. Class II General Controls and Special Controls (i.,e. powered wheel chair, pregnancy test)
    - With Exemptions
    - Without Exemptions
3. Class III General Controls and Premarket Approval (i.e. Pacemakers, implants, prostheses)

The class to which your device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market. If your device is classified as Class I or II, and if it is not exempt, a 510k will be required for marketing. All devices classified as exempt are subject to the limitations on exemptions. Limitations of device exemptions are covered in 21 C.F.R. Parts 862.9, 863.9, 864.9, and 865.9. For Class III devices, a premarket approval application (PMA) will be required unless your device is a preamendments device (on the market prior to the passage of the medical device amendments in 1976,

or substantially equivalent to such a device) and PMA's have not been called for. In that case, a 510k will be the route to market.

If your device is a type that requires a premarket notification (or 510(k)) submission, you are required to submit a 510(k) when the following occurs: (a) a foreign manufacturer intends to export a medical device to the U.S. that the firm has never before shipped to the U.S.; (b) either the foreign manufacturer or initial distributor changes the intended uses of devices that are legally being marketed in the U.S.; or (c) changes or modifications to a legally marketed device that could significantly affect its safety or effectiveness.

Device classification depends on the *intended use* of the device and also upon *indications for use*. For example, a scalpel's intended use is to cut tissue. A subset of intended use arises when a more specialized indication is added in the device's labeling such as, "for making incisions in the cornea". In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Class I includes devices with the lowest risk and Class III includes those with the greatest risk.

Devices must meet FDA regulations prior to the importation of medical devices into the United States. FDA does not recognize regulatory approvals from foreign countries/areas.

All foreign firms are required to both register their establishments, identify a U.S. Agent, and individually list their devices before they may import them into the United States.

The data elements below are recommended to be submitted by the importer/broker/filer for device entries:

A) Commercial Description
B) FDA Manufacturer
C) FDA Shipper
D) FDA Country of Origin
E) FDA Product Code – For assistance in determining the correct FDA product code for a medical device access the FDA's Center for Devices and Radiological Health website to search the medical device database: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm

   Search the database for the device being imported. Look for product code designated in Medical device database. This product code may appear as a partial or complete code of the FDA product Code. Use this code as a starting point to determine the correct FDA Product Code.

   Per Guidance for Industry and Food and Drug Administration Staff Medical Device Classification Product Codes issued April 11, 2013 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM285325.pdf), the use of Classification Product Codes in Post Market Review in relation to Imports is as follows:

   Import/Export

   1. Office of Regulatory Affairs (ORA) Product Code Builder

   In order to ensure that a medical device is in compliance with FDA regulatory requirements, importers/brokers/filers are required to submit certain import information. One data element that is required to be provided is the product code. If the product code is unknown, importers/brokers/filers can use the Office of Regulatory Affairs' (ORA) Product Code Builder (http://www.fda.gov/ForIndustry/ImportProgram/ProductCodeBuilderforFoods/default.htm) to formulate a product code for the product they are importing. In addition, the CDRH (Center for Devices and Radiological Health) Product Classification Database (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm) can be used to look up a device's definition and regulatory requirements, neither of which is provided in the ORA Product Code Builder. As new product codes are created by CDRH and old ones modified, ORA's Division of Compliance Systems (DCS) is notified, and the Product Code Builder is updated. The product code used for the FDA import admissibility review process is formatted differently than the classification product code used by CDRH. There is no definitive meaning for the three digit classification product codes in CDRH's Product Classification Database. However, ORA's Product Code Builder uses a seven digit product code, rather than the three letter combination found in the

product code database. The seven digit product codes encompass devices, foods, drugs, biologics, and cosmetics and each digit signifies a particular description. For example, FRN is the product code assigned to Pump, Infusion in CDRH's Product Classification Database. The same product code translates to 80F--RN in ORA's Product Code Builder. The two numbers at the beginning of the seven-digit product code represent the medical specialty panel classified for the device.

2. Import Entry Process

The classification product code helps the FDA import entry reviewer determine what information he/she should verify to ensure the medical device meets all FDA regulatory requirements (e.g., registration, listing, clearance/approval numbers).

Classification product codes are also used by FDA to designate products for Import Alerts. Import Alerts identify problem commodities, shippers and importers, and provide guidance for import coverage.

F) Quantity
G) Value
H) Consignee
I) FDA Facility Registration number or DUNS – to obtain the medical device manufacturer's establishment registration number, access the following database: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm

J) Affirmation of Compliance codes and qualifiers:

Per the Letter to Industry about Import Entry Review Process dated March 24, 2011 (http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm248321.htm), providing complete AofC information for devices expedites the FDA release process. Each entry line should contain an AofC code for:

- Device Foreign Manufacturer (DEV) or Device Foreign Exporter (DFE)
- Device Listing (LST)
- Device Initial Importer (DII)
- Premarket Application (PMA) (Can be a PMA, a Humanitarian Device Exemption (HDE), or a Product Development Protocol (PDP) number) OR a Premarket Notification Number (PMN) OR an Investigational Device Exemption (IDE)

Additional AofC codes can be provided as considered necessary. Use of these codes affirms that the product identified in a USFDA import entry line meets USFDA requirements specific to the product. While use of these AofC codes is voluntary, transmission will help expedite the entry review process and increase the likelihood that your shipment may be processed based on import system screening and is not held for further USFDA entry review. Each code listed should only be used once per entry line.

CODE TITLE/DESCRIPTION

CPT Device Component

This code should be used when importing a component of a device that requires further processing or inclusion into the finished device. This code is not to be used if the device component is classified by FDA as a finished device, e.g., wheelchair component. Whenever CPT is used, you should also provide the AofC DII.

DEV Device Foreign Manufacturer Registration Number

This code and qualifier should be the device registration number issued by CDRH for the firm manufacturing the product identified in the FDA line.

DFE Device Foreign Exporter Registration Number

The code and qualifier should be the device registration number issued by CDRH for the exporter who exports or offers for export to the United States (U.S.), a device manufactured or processed by

another individual, partnership, corporation or association in a foreign country, as well as devices originally manufactured in the United States.

DII Device Initial Importer Registration Number

The code and qualifier should be the device registration number issued by CDRH for the importer who takes first title to devices imported into the U.S. The initial importer of the device must register its establishment with FDA. An initial importer is any importer who furthers the marketing of a device from a foreign manufacturer to the person who makes the final delivery or sale of the device to the ultimate consumer or user, but does not repackage, or otherwise change the container, wrapper, or labeling of the device or device package.

IDE Investigational Device Exemption Number

This code and qualifier should be the investigational device exemption number issued by CDRH for the product identified in the FDA line. An IDE number begins with the letter “G”.

IFE Import for Export

This code allows for importation of noncompliant articles (including drug and device components, food and color additives, and dietary supplements) under the new import for export provisions of the FD&C Act [801(d)(3)(a)]. The article must be incorporated, by the initial owner or consignee, (which can be someone other than the importer of record) into a product for export. The product must be exported from the United States by this initial owner or consignee in accordance with the provisions of Section 801(e) and 802 of the FD&C Act or 351(h) of the PHS Act. No qualifier is required but QUANTITY AND VALUE MUST BE TRANSMITTED when using this AofC.

IRC Impact Resistance Lens Certification

This code is used to certify that the filer/importer has on hand the test results or a certificate that shows that the product on the FDA line has met the standards for impact resistance lens. See list of product codes in attachment, which require the use of this AofC.

LST Device Listing Number

The code and qualifier should be the device listing number issued by CDRH for the product identified in the FDA Line.

LWC (Electrode) Lead Wire or Patient Cable

This code is used when importing electrode lead wires, patient cables, or devices that use them. The affirmation means that (1) the device shipment does not contain any pre-wired electrodes, electrode lead wires, or patient (transducer) cables, or (2) any pre-wired electrodes, electrode lead wires or patient cables comply with 21 CFR 898, Performance Standard for Electrode Lead Wires and Patient Cables. See list of product codes in attachment, which require the use of this AofC.

MDL Model Number

The code and qualifier should be the manufacturer’s model number or catalog number for the product identified in the FDA line.

PMA Device Premarket Approval Number

This code and qualifier should be the Device Premarket Approval (PMA) number, product development protocol (PDP) number or Humanitarian Device Exemption (HDE) number issued by CDRH for the product identified in the FDA line. A PMA number begins with the letter ‘P’, a PDP number begins with the letter ‘D’, and a HDE begins with the letter ‘H’.

PMN Device Premarket Notification Number (510(k))

This code and qualifier should be the device premarket notification (510(k)) number issued by CDRH for the product identified in the FDA line. A PMN number begins with the letter ‘K’.

CODE - QUALIFIER EXAMPLES

Note: Should always be the DEV associated with the foreign manufacturer and not the US Specifications Developer.

DEV - 3003999999 or 9610123
DII - 3003999999 or 1021365
PMA - P001234
IDE - G01232
DFE - 3003999999 or 9710123
LST - E100100
PMN - K011234
MDL - 650 -182

If you have any questions about the import entry review process for medical devices or any general questions regarding the entry screening process, contact the CDRH Office of Compliance Import/Export Safety Staff at cdrhocimport@fda.hhs.gov. If you have questions related to a specific detained entry, you must first contact the Import Compliance Officer in your local USFDA District Office and reference the entry number for assistance.

9. Vaccines and Biologics – CBER Products

CBER regulates biological and related products, including blood and blood products (which includes certain kinds of devices), vaccines, allergenics, tissues, and cellular and gene therapies. CBER also regulates the medical devices involved in the collection, processing, testing, manufacture and administration of licensed blood, blood components and cellular products and 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 order to import a CBER-regulated product into the United States, the product must meet FDA's regulatory requirements.

At the time of importation, the customs broker will transmit several data elements to the FDA. This could include, but not limited to: description, manufacturer MID, FDA product code, and Affirmation of Compliance codes with Qualifiers.

The FDA product code is a seven character alphanumerical code that helps FDA classify and review imports. The first part is the "Industry Code." The Industry Code for all CBER-regulated products is the number "57," so the FDA Product Codes for all CBER-regulated products begin with "57".

Check here to determine the proper FDA product code: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/BiologicsImportingExporting/UCM196892.pdf

If the product code is not found in the CBER table you can construct it using the FDA's product code builder application. See Appendix B for the hyperlink.

A BLA (Biological License Application) can be either under CDER or CBER jurisdiction. As CDER administers the PLAIR process (See PLAIR section 11b), FDA will only allow BLAs under CDER's jurisdiction to participate in the PLAIR program.

Another difference between importing CDER versus CBER regulated material is that there appears to be no mechanism to list the CBER drug product under the foreign manufacturer in the FDA's e-drug listing system. Therefore, only the NDC code can be provided as an Affirmation of compliance code and not the DLS code.
The recommended affirmation of compliance codes for CBER regulated products are as follows:

AoC:	Qualifier:
REG	Manufacturer's site registration number
REG	Manufacturer's DUNS number

BLN	Biological License number (US Government License Number – as it appears on product labeling. Each firm has one government assigned biological license number)
STN	Submission Tracking Number (This is the Biological License Application BLA number)
NDC	National Drug Code (if importing finished goods or may be requested by various ports when importing intermediates, bulk drug substances or drug products)

You can send questions pertaining to the importation of CBER-regulated products to CBERImportinquiry@fda.hhs.gov

10. FDA Review Statuses and Responding to FDA Detention

10a. FDA Review Statuses

The following statuses are transmitted through ABI and represent the review stages an entry may proceed through during its review by the FDA.

FDA Review: This status indicates the entry is proceeding through electronic review of information by the FDA.

FDA Docs Required: FDA has requested physical documents indicating discrepancies found in the electronic review.

FDA Exam Sample: Notification that FDA may have physically sampled the product.

FDA Exam / Exam Notify: Entry is pending FDA review or FDA may be requesting availability for physical examination of the entry. This may include a label examination or sampling of the product. Note: some ports are now demanding re-delivery of material through CBP if the entry has been moved out of the immediate area of the port of entry. Past references to the “50 mile” rule may not apply. This is not recognized as a reasonable or established distance by the FDA. If the product has been moved from the port of entry, the importer must comply with CBP Mark and/or Re-delivery (CBP form 4647) request, or contact FDA to determine examination or re-delivery requirements.

FDA Detained: The entry is subject to refusal because the product is not in compliance (typical FDA wording is “appears to be mis-branded or adulterated”).

In addition to FDA statuses transmitted through ABI, OASIS will generate a "Notice of FDA Action," which will provide more specific information on the actions taken broken down by each entry line (e.g., "sample collected" or "intended for sampling", "detained", "released", or "refused"). As the status changes for a particular line, a new "Notice of FDA Action" will be issued to advise the appropriate individuals of the changes. The use of the designation "Product Collected by FDA," "Detained," "Released," "Refused," or similar language on the "Notice of FDA Action," should be considered as satisfying the requirements of the law for "giving notice thereof to the owner or consignee."

Note: It is important to work with your broker so that they deliver the detention notices in a timely fashion and to the appropriate group.

10b. Responding to FDA Detention

The FDA has the right to detain shipments upon review of the entry if the importer has not provided the required information for the FDA to make a determination that the required laws and regulations for the import of the drug have been satisfied. The shipment status is noted "FDA DETAINED", and is first visible in the broker entry screen through ABI. A hard copy of the Notice of FDA Action is mailed from the FDA District Office to the Importer of Record and the ultimate consignee if they differ from the importer of record identified in the entry documentation and can be obtained by the broker.

Note: With repeat notices it is especially important to work with your broker so that they deliver the detention notices in a timely fashion and to the appropriate group.

The Notice of FDA Action - Detention Notice states the date that a response must be received by the FDA. If a response is not received by the date specified, the FDA has the right to change the status of the shipment to "FDA REFUSED" which may require the shipment to be destroyed under the supervision of CBP or exported at the expense of the importer.

When responding to an FDA Detention it is recommended to fully review the Notice of FDA Action and a copy of the broker entry screen, and copies of the documents that accompanied the shipment, such as invoices, packing lists, etc. Determine the specific documentation to be included with your response to clarify to FDA that the shipment meets the law and regulations for importing drug. It is important to keep in mind the magnitude of shipments the FDA processes. As such they cannot be familiar with individual company naming conventions, and terms. The FDA review relies on the data in MARCS, the documentation with the shipment, the drug listing and other FDA internal databases.

In your response it is helpful to remember to include the following:

- The Customs Entry Number – (Note this identifies the specific shipment)
- Corrections to any errors in the entry documentation
- The intended end use of the drug and the final disposition of product.
- Provide supportive documentation referencing the specific regulatory submission which would clarify that your company has filed the appropriate NDA, ANDA, IND, amendment, or supplement.
- Provide supportive documentation to clarify the name of the drug if a drug has had several names in the development process.
- Provide supportive documentation to clarify any changes submitted in an Annual Report (i.e. legal entity name change), since this information is not accessible in the databases utilized by FDA Port personnel.
- As directed on the Notice of Action, FAX or e-mail the response to the Compliance Officer identified on the Notice of FDA Action or specific e-mail address of the FDA Port of entry. Include the Customs Entry number on all correspondence. In addition, upload the response in ITACS.
- Educating your broker on the process and your products is a good practice.

After the requested information is submitted to the FDA Compliance Officer listed on the detention notice, the shipments still remains under detention. The FDA has 90 days to respond. Follow-up communications can be conducted via phone, Fax, or some ports have a Help Line or dedicated e-mailbox. The contact information is noted on the Notice of FDA Action or can be found on the FDA website. Note: The shipment may be delivered to the consignee, but the shipment cannot be opened until you receive a "May Proceed" or “Released” status. Consider the use of a company Quality Assurance (QA) hold or a similar mechanism to assure product is not released to further manufacturing or the market.

In OASIS, the following are definitions used to describe "May Proceed" or "Release" actions:

May Proceed: "Product may proceed without FDA examination. FDA has made no determination the product complies with all provisions of the Food, Drug, and Cosmetic Act or other related acts. This message does not preclude action should the article later be found violative." (No compliance decision has been made.)

Release: "The product is released after FDA examination.” This message does not constitute assurance the product complies with all provisions of the Food, Drug, and Cosmetic Act or other related acts and does not preclude action should the article later be found violative." (A compliance decision has been made.)

11. Import Alerts

FDA Import Alerts, also called FDA automatic detentions, exist to call attention to foreign products or firms that appear to be in violation of the Food Drug and Cosmetic Act (FD&C ACT). When a foreign manufacturer is placed on the “Red list”, their imported products are automatically detained by the FDA, via a process called Detention Without Physical Examination (DWPE), until the company removes itself from the Import Alert.

Importing products from companies found on a red list will involve providing documentation, suitable to the nature of the alert, which gives evidence that the shipment is compliant with applicable regulations. For instance, a DWPE under Import Alert 66-66: “API’s That Appear To Be Misbranded Under 502(f)(1) Because They Do Not Meet The Requirements For The Labeling Exemptions in 21 C.F.R. 201.122” may require an End Use Letter indicating the approved NDA or ANDA of the drug product for which the API is intended and may require a sample of the labeling to show that it contains the appropriate “Caution…” statement and “Rx only” statement.

Each Import Alert provides a reason for the alert and the means by which to obtain entry for the articles or to obtain removal of the foreign manufacturer from the red list.

There are over 150 FDA Import Alerts affecting food products, drugs and medical devices. They are categorized by the products they address and are identified by the Alert Number, a 4 or 5 digit number unique to the specific nature of the import violation. Please see the following table for a list of Import Alerts pertaining to drug products and medical devices:

Drug Product Import Alerts

Number	Import Alert Type	Publish Date	Import Alert Name
66-41	DWPE	03/15/2012	Detention Without Physical Examination of Unapproved New Drugs Promoted In The U.S.
66-40	DWPE	03/09/2012	"Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs"
66-66	DWPE	01/30/2012	"APIs That Appear To Be Misbranded Under 502(f)(1) Because They Do Not Meet The Requirements For The Labeling Exemptions In 21 CFR 201.122"
66-38	DWPE with Surveillance	01/12/2012	"Skin Care Products Labeled As Anti-Aging Creams"
66-43	DWPE	11/29/2011	"Detention Without Physical Examination of THA" (Investigational New Drug)"

Medical Device Import Alerts

Number	Import Alert Type	Publish Date	Import Alert Name
89-01	DWPE with Surveillance	11/28/2011	"Electrical Muscle Stimulators and Iontophoresis Devices"
89-04	DWPE	03/12/2012	"Detention Without Physical Examination Of Devices From Firms That Have Not Met Device GMP's"
89-09	DWPE	10/12/2011	"Detention Without Physical Examination of Liquid Injectable Silicon (LIS) Labeled Medical Grade Or Intended For Medical Use"
89-08	DWPE	03/09/2012	"Detention Without Physical Examination of Class III Devices Without Approved PMA's Or IDE's and Other Devices Not Equivalent or No 510k"
89-06	DWPE	03/18/2011	"Detention Without Physical Examination Of 'Super Pulse' Electronic Devices"
89-07	DWPE	03/18/2011	"Detention Without Physical Examination Of Gynecological Devices Manufactured By Leiban International"
89-10	DWPE	03/18/2011	"Detention Without Physical Examination of Implantable Devices Made from Proplast"

89-11	DWPE	03/18/2011	"Detention Without Physical Examination of Class III Devices Without PMAs or PDPs"
89-13	DWPE	03/18/2011	"Detention Without Physical Examination of Electrode Lead Wires and Patient Cables That Do Not Comply With the Applicable Performance Standard"
89-16	DWPE	03/13/2012	Detention Without Physical Examination of Products from Medical Device Firms Refusing FDA Foreign Establishment Inspection

Each import alert is updated from time to time to accurately reflect a list of violative companies. To see an updated list of import alerts, please refer to the following website: http://www.accessdata.fda.gov/cms_ia/iapublishdate.html .

12. Special Situations

12a. Import For Export (IFE)

When a drug or device component, food additive, color additive, or dietary supplement is imported under section 801(d)(3) of the FD&C Act, the importer is required to submit a statement to FDA at the time of each importation with the following information:

Chain of Custody Letter

1. Statement identifying that such article (the components, parts, accessories, or articles) is intended to be further processed by the initial owner or consignee; or, incorporated by the initial owner or consignee into a drug, biological product, device, food, food additive, color additive, or dietary supplement that will be exported from the United States by the initial owner or consignee in accordance with section 801(e) or section 802 of the FD&C Act or section 351(h) of the PHSA. Simply storing an article or product in the United States before export is not considered "further processing." The intent of the use of the material cannot be change once the article is imported.
2. Identification of the manufacturer of such article and each processor, packer, distributor or other entity that had possession of the article in the chain of possession from the manufacturer to such importer of the article.
3. Identification of all entities that had possession of the article in the chain of possession should include information sufficient to accurately identify the entity such as the name of each entity (including business and trade names), complete physical address, transaction dates, and any other information to aid in identification such as telephone and fax number, and e-mail address.

Note: Supply Chain maps that detail the transportation mode, lane route, the AofC, broker, and other appropriate supply chain information are a good practice and soon to be required as part of a site's "supply chain integrity" program.

Additional Requirements

1. Certificates of analysis (CofA), as are necessary to identify the imported article, must accompany the statement. The submission of such certificates is not required if the imported article is a device or is an article described in 801(d)(4) (blood or blood components). Certificates of analysis, or equivalent documentation should provide the article's formulation, ingredients, components, or assay, as appropriate to the type of article.
2. At the time of initial importation and before delivery to the importer, initial owner, or consignee, a bond must be executed providing for liquidated damages in the event of default, in accordance with U.S. CBP requirements. Temporary Import Bond (TIB), Consumption, or Warehouse Bond:
    a) Consumption Entry Bond Type – typically results in detention of the imported article. (If CBP/IFE entry is automatically released, it is advisable to confirm the release of the entry with the FDA.) Article may be processed while on detention. FDA requirements for close

out of the entry vary. Supervision by FDA may be required at the time of export. Article needs to be exported/destroyed within 314 days from the date of import, unless an extension is requested and granted by the FDA. Note: When the importer notifies the District that all IFE material has been exported/destroyed, upon District verification, the entry will receive a "Release with Comment" status indicating violative articles have finished IFE processing.

b) TIB / IFE – entry is typically released by FDA. The imported article can remain in the U.S. for 1 year, with the option of renewing the TIB for two, one year intervals resulting in a maximum of three years of processing time.

3. The initial owner or consignee of the article must maintain records of the use and/or destruction of such imports and must submit the records or a report to FDA upon request. Note: Reference the Notice of FDA Action for the specific District's export requirements of the IFE material.
4. The initial owner or consignee must destroy any article or portion not used in an exported product.

Broker Requirements

For electronic entry submissions through the CBP Automated Commercial System (ACS) to the FDA:

1. Provide the name of initial owner or consignee in the FDA consignee field using the appropriate FDA Facility Establishment Identifier (FEI) number.
2. When the article is intended for multiple owners or consignees, a separate FDA line should be created for each owner or consignee as provided for in the ACS system.
3. Transmit the Affirmation of Compliance (AofC), identified by the code "IFE" (Import for Export).
    a. Use of the "IFE" affirmation triggers prompts for the submission of Quantity and Value data. If any of this information is not provided, the notification will be considered incomplete by the system. Such lines with "IFE" (or any Affirmation) will display the Affirmation in the Entry Line Summary and line detail screen. If electronic submission is made, in most cases it is unlikely that all of the information required under section 801(d)(3) will be able to be provided through electronic entry. Districts should request and review the supporting paper entry documents for all "IFE" entries.
4. Submit Chain of Custody Letter and Certificates of Analysis as necessary

For manual entry submissions, or when FDA has requested supporting paper entry documents for an electronic "IFE" entry, all documentation should be included in the filer's entry package including:

1. Chain of custody letter
2. Certificate of analysis as necessary

Reference the link below for specific FDA guidance on the IFE requirements.

http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074300.pdf

12b. Pre-Launch Activities Importation Request (PLAIR)

Under the PLAIR program, FDA exercises its enforcement discretion allowing the import and warehousing of unapproved finished drugs with an original, pending NDA or ANDA in preparation of the market launch.

The following informal guidance on PLAIRs has been issued by the FDA: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ImportsandExportsCompliance/UCM365538.pdf

The PLAIR request should contain:

- The drug product name (trade and established) and how supplied (complete product description).
- The name of the CDER Office of New Drugs or Office of Generic Drugs project manager assigned to the pending original application.
- The National Drug Code (NDC) number, if assigned.
- The name, address, registration number, and telephone number of the foreign manufacturer of the finished dosage form drug product.
- The name, address, registration number, and telephone number of the U.S. consignee.

- The application number for the finished dosage form drug product that is pending approval by FDA.
- The name, address, registration number, and telephone number of the warehouse or the distribution facility controlled by or under contract with the applicant where the finished dosage form drug product in final packaged form will be stored pending approval. This facility should be identified in the pending application.
- When a finished dosage form drug product in bulk is imported for minimal further processing, information regarding the facility where minimal further processing activities will occur, including (1) the name and address of the facility, (2) a description of the further processing activities, (3) information about where the unapproved finished dosage form drug product in final packaged form will be stored pending approval, and (4) the registration number. This facility should be identified in the pending application.
  (i) A letter signed by an authorized representative of the applicant certifying under 18 U.S.C. 1001 that neither the applicant nor its consignees or distributors will sell, offer for sale, or distribute this drug product in U.S. commerce until FDA approval is effective.

Additional information:

- The PLAIR request should be submitted via email to, CDER-OCPLAIR@fda.hhs.gov
- The applicant should include in the subject line the application number and drug product name.
- The PLAIR should be submitted a minimum of 30 days prior to the arrival of the shipment but no more than 60 days prior to anticipated NDA/ANDA approval.
- The PLAIR application should contain the actual import quantities
- A PLAIR can only be submitted for an original, pending NDA/ANDA
- A PLAIR pertains to unapproved finished drug product. A PLAIR cannot be used for Active Pharmaceutical Ingredient (API) or bulk drug ingredient
- A PLAIR cannot be used for pending supplements (PAS, CBE-30, CBE-o) to an existing, approved NDA/ANDA or new strengths/presentations associated with an approved NDA/ANDA.
- The PLAIR pertains to CDER regulated products only (including CDER regulated BLA products).
- Only one PLAIR can be submitted for each original new drug application
- The PLAIR must be submitted by the NDA/ANDA sponsor/applicant holder on firm letterhead
- The foreign drug product manufacturer must be registered, have a satisfactory GMP inspection and qualifying facility inspection.
- The firm must be registered and the drugs must be listed once the application is approved.
- Under the approved PLAIR, only one import entry (regardless of the quantity, batches or lot numbers offered for import) will be granted for the initial market launching

After receipt of the PLAIR request, the PLAIR group will confirm the GMP status of the manufacturer and reach out to the Office of New Drugs (OND) or Office of Generic Drugs (OGD) to confirm if there are any CMC (Chemical Manufacturing Control) issues. The PLAIR group will notify the applicant whether the PLAIR request is acceptable. The time period between submission and acceptance may vary, but averages approximately 10 business days. If the PLAIR request is approved, an e-mail confirmation will also be provided to the Division of Import Operations (DIO) and the Office of Regulatory Affairs (ORA), informing both groups that the PLAIR request is acceptable.

Once a PLAIR has been granted, the applicant should provide the Customs entry number in advance of shipment arrival to DIO (DIOPPLAIR@fda.hhs.gov). DIO will notify the District at the port of entry that the shipment associated with the approved PLAIR may be released and allowed to proceed into the country using enforcement discretion.

The PLAIR must be amended to reflect any extra volume shipped. This can be done by sending the amended PLAIR directly to CDER-OC-PLAIR@fda.hhs.gov for approval.

The PLAIR may be denied if there is any application or product concerns, or premature submission of the PLAIR. The applicant does not need to re-submit the PLAIR, but can follow-up in 30-45 days.

To close out an approved PLAIR the applicant must send the NDA approval letter to CDER-OCPLAIR@fda.hhs.gov.

A PLAIR draft guidance was published by FDA in July 2013. Industry provided substantial comment. To date FDA has not finalized the draft guidance.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM362177.pdf

12c. Foreign Trade Zone (FTZ)

A FTZ may be used for many purposes, including the deferral of duty payment until goods are offered for Customs entry out of the FTZ. Other uses for FTZs include manufacturing, warehousing, packaging, labeling, and inspection. CBP considers FTZs to be outside of the Customs territory of the U.S. The FDA considers FTZs to be within "interstate commerce," but goods admitted into FTZs are not considered "imported or offered for import." The FDA regulates goods admitted into FTZs under its domestic authority, and does not apply Section 801 until admitted goods are offered for Customs entry. The FDA OASIS interface does not request information at the time of FTZ admission, but requests information at the time Customs entry is filed.

12d. American Goods Returned

The FDA Regulatory Procedures Manual – Chapter 11 defines AMERICAN GOODS RETURNED as: Goods produced in the United States (U.S.) which, after being exported, are subsequently returned to the U.S. Such goods are considered imports.
In accordance with FD&C Act 801 (d) (1), which states, "*Except as provided in paragraph (2) and section 384 of this title, no drug subject to section 353(b) of this title or composed wholly or partly of insulin which is manufactured in a State and exported may be imported into the United States unless the drug is imported by the manufacturer"*, API and drug product originally exported out of the US can only be returned to the original manufacturer (manufacturing location) .

While the FD&C Act allows the return of US manufactured material to the US manufacturer, there are 2 Import Alerts which emphasize the suspect and violative nature of American Goods Returned. Import Alert #99-01, "Surveillance of American Goods Returned" and Import Alert #66-14, "Re-importation of All Prescription Drugs for Human Use", both offer additional guidance to FDA port personnel when reviewing American Goods Returned products. The Import Alerts suggest the material should be examined and laboratory tested if appropriate. CDER assistance is suggested when appropriate.

Section 801 (d) (1) of the Act does not preclude the US manufacturer from conforming with section 801(a) of the Act. Therefore once the district confirms the material is being returned to the US manufacturer, the normal entry review process should follow confirming the material is not adulterated, misbranded or in violation of 801(a) of the Act. Simply stated, this means the material must also be US approved material for the normal import review process to occur.

For the return of US approved material, it is recommended that an End Use letter is prepared detailing the following information: the drug name, strength, dosage type, the manufacturer's name and address, the manufacturer's FEI number, the NDA number, NDC number, the reason for the return and what the final disposition of the returned material will be. The End Use Letter should be written by the U.S. importer on its letterhead and contain a hand written signature. The letter should be proactively provided to the FDA and may be uploaded via ITACS at the time of entry filing.
If the material being returned is not US approved material and would be considered misbranded or adulterated (e.g. product labeled in a foreign language, material manufactured to foreign specifications and not compliant with U.S. specifications, no approved NDA), the entry should be declared as an Import for Export (IFE). Refer to the Import for Export section.

When declaring an import to CBP as U.S. Goods Returned, there are additional Customs (CBP) requirements. Refer to 19 C.F.R. Part 10_Articles Conditionally Free, Subject To a Reduced Rate, etc. and consult with your customs broker.

12e. FDA Prior Notice (PN)

The Food & Bioterrorism Act of 2002 was implemented by the FDA in December of 2003 through an Interim Rule to enhance food safety following the events of September 11th. Although food is the main focus of this Act, some pharmaceutical imports are considered food or food related (e.g. pharmaceutical grade soybean oil) and are covered by the Act. This Act requires an electronic submission of a pending food import not more than 10 days before arrival in the US and not less than:

- Two hours before arrival by land via road,
- Four hours before arrival by air or by land via rail; or
- Eight hours before arrival by water.

Prior notice is usually filed by the customs broker through ABI, but may be filed by anyone with knowledge of the required information through the FDA PN System Interface at www.access.fda.gov.

The PN requirement is tied to the HTSUS declared for the import. Reference this website to determine if the HTS code for the import requires PN. http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/PriorNoticeofImportedFoods/ucm170031.htm Prior notice is required for FD4 tariff codes, while prior notice may be disclaimed in some cases for FD3 tariff codes.

FD4 Prior Notice Required

When PN is required, the following information must be included in the prior notice:

- Identification of the submitter
- Identification of the transmitter (if different than the submitter)
- Entry type and CBP identifier
- The identification of the article of food, including complete FDA product code, the common or usual name or market name, the estimated quantity described from the smallest package size to the largest container, and the lot or code or other identifier (if applicable)
- The identification of the manufacturer
- The identification of the grower, if known
- The FDA country of production
- The identification of the shipper, except for food imported by international mail
- The country from which the article of food is shipped or, if the food is imported by international mail, the anticipated date of mailing and country from which the food is mailed
- The anticipated arrival information (location, date, and time) or, if the food is imported by international mail, the U.S. recipient (name and address)
- The identification of the importer, owner, and ultimate consignee, except for food imported by international mail or transshipped through the U.S.
- The identification of the carrier and mode of transportation, except for food imported by international mail
- Planned shipment information, except for food imported by international mail. (See note on supply chain maps.)

The identification codes required are the eleven digit FDA facility registration code (FEI number) that is specifically for FDA Prior Notice. Some foreign facilities may have a ten digit code.

FD3 Prior Notice May Be Required

When an import is FD3, a review is required to determine if it is considered a “food” by the FDA Interim Rule. If so, follow the steps outlined above for FD4. If not, the filer may omit the PN declaration. In these cases, it is advisable to maintain a letter on file documenting the decision to disclaim FDA PN for internal recordkeeping or the FDA if requested.

Appendix A: Constructing the Manufacturer Code

These instructions provide for the construction of an identifying code for a manufacturer or shipper from the name and address. The code can be up to 15 characters in length, with no inserted spaces. However, it may be thought of as five "pieces" as follows:

COUNTRY (Piece 1: 2 characters)

Use the ISO code for the country, such as "PE" for Peru.

MANUFACTURER NAME (Pieces 2 and 3: up to 3 characters each)

Use the first three characters from each of the first two words of the name. There will be no third piece if the name is one word. Amalgamated Plastics Corp. would give "AMAPLA"; Bergstrom would give "BER". If there are two or more initials together, treat them as a single word. For example, ABC Company, A.B.C. Company, or A B C Company would all yield "ABCCOM."

- Note: soon to come as an address location will be the GS1 standard attribute identifier called “Global Location Number (GLN)” www.gs1.org

ADDRESS LINE WITH STREET NAME and/or BOX NUMBER (Piece 4: up to 4 characters)

Find the largest number on this line and use up to the first four digits. For example, 11455 Main Street Suite 9999 would yield "1145". A suite number or a post office box should be used if it contains the largest number. However, use no number in the case of One Hundred Century Plaza. There will be no fourth piece if there is no numeric on the address line.

When numbers are separated by commas or hyphens, ignore all punctuation and use the number that remains. For example, either "12,34,56 Akasaka Road" or '12-34-56 Akasaka Road" would yield "1234". Note that the address line on the invoice may be after the line containing the city and zip code (or equivalent). For example, German invoices frequently place the city and its numeric code before the street address. Be sure to identify the address line numeric and use it, not the city numeric.

CITY (Piece 5: up to 3 characters)

Use the first three letters from the city name. Tokyo would be "TOK," St. Michel would be "STM."

Apply these general rules to construct a manufacturer code

1) Ignore all punctuation, such as commas, periods, ampersands.
2) Ignore all single character initials, such as the "S." in Thomas S. Delvaux Company.
3) Ignore the English words "a", "an", "and", " of", "the".
4) In the case where multiple company names and/or addresses appear on the invoice, use the name and address associated with the corporate headquarters as opposed to the division, office, etc.

Here are some examples of manufacturer names and addresses and their codes:

LA VIE DE FRANCE
243 Rue de la Payees
62591 Bremond, France

FRLAVIE243BRE

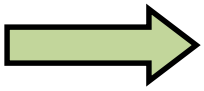
20TH CENTURY
TECHNOLOGIES
5 Ricardo Munoz, Suite 5880
Caracas, Venezuela

VE20TCEN5880CAR

THE E.K. RODGERS COMPANIES
One World Trade Center
London, England SWLY 5HQ

GBEKRODLON

THE GREENHOUSE
45 Royal Crescent



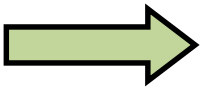
USGRE45BIR

Birmingham, Alabama, 35204

CARDUCCIO AND JONES
88 Canburra Avenue
Sydney, Australia

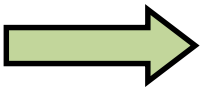
AUCARJON88SYD

N. MINAMI & CO.,LTD.
2-6, 8-Chome Isogami-Dori
Fukiai-ku
Kobe, Japan



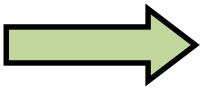
JPMINCO268KOB

BOCCHACCIO S.P.A.
Via Mendotti, 61
8320 Verona, Italy



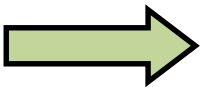
ITBOCSPA61VER

MURLA-PRAXITELES INC.
Athens, Greece



GRMURINCATH

SIGMA COY E.X.T.
1640 Delgado
4000 Smyrna, Italy



ITSIGCOY1640SMY

Appendix B: FDA Product Code Builder

FDA Product Codes may be identified by going through the tutorial offered by the FDA at:

http://www.accessdata.fda.gov/scripts/ora/pcb/tutorial/tutorial.cfm .

Once capable of building a product code, the application can be found at: http://www.accessdata.fda.gov/SCRIPTS/ORA/PCB/PCB.HTM .

- Note: once you've built an FDA PC for a specific product – record the decision process and result in your import database.

The product code builder covers the following industries:

Pharmaceutical Necessities and Containers for Drugs and Biologics (Industry Code 55)

Antibiotics (Industry Code 56)**:** Antibiotics are coded under Industry Code 56. This includes antibiotics for humans and animals. Examples of common antibiotics include, but are not limited to, natural or synthetic penicillin, tetracycline, neomycin, streptomycin, and erythromycin.

The manufacturer's information will direct the Product Class decision. Scientific and medical terms are used to describe the Product Classes. The Subclass categories differentiate between human and animal antibiotics. PICs are the same as those used for Human Drug products.

Code multi-ingredient products under the product class of the ingredient that is listed first in the product labeling active ingredient list. A list of active ingredients is required on the product label (e.g. triple ointment). Use the appropriate subclass for multi-ingredients based on whether the product is for humans or animals.

If the product contains a drug or antibiotics as well as dietary supplement ingredients, it should be coded as a drug or antibiotic, not a dietary supplement.

Glossary

- Antibiotic Drug: A substance, such as penicillin or streptomycin, produced by or derived from certain fungi, bacterial, and other organisms that can destroy or inhibit the growth of other microorganisms. Antibiotics are widely used in the prevention and treatment of infectious diseases.
- Rx: A prescription drug. Under Industry Code 56, this is a prescribed antibiotic.
- Non-Rx: Under Industry Code 56, this refers to an antibiotic that can be obtained without a prescription.
- Diagnostic Invitro: For diagnostic use outside the body, not for therapeutic use.

Biologics and Licensed In-Vivo and In-Vitro Diagnostic Products (Industry Code 57): Biologics and licensed in-vivo and in-vitro diagnostic products are coded under Industry Code 57. A biologic is synthesized from living organisms or their products and used medically as a diagnostic, preventive, or therapeutic agent and includes both biological products, as defined in the Public Health Service (PHS) Act, and tissues. Biologics for animals are not regulated by the FDA, but are regulated by the U.S. Department of Agriculture (USDA). Examples of common biologics for human use include, but are not limited to, human blood and blood products, vaccines, tissue products and licensed in-vitro diagnostic products.

There is a unique set of Subclass codes for biologics and licensed in-vivo and in-vitro diagnostic products, but Process Indicator Codes (PIC) are not used. Although no Process Indicator Code is used in this Industry by FDA OASIS and FACTS users, filers must transmit a dash "-" on the PIC field. The Product Code Builder Application will return a dash automatically.

Glossary

- Biologic: A biologic is produced from living organisms or their products and used to diagnose, prevent or treat a medical condition.
- Licensed In-Vitro Diagnostic Product: A licensed in-vitro diagnostic product (1) is used for in the treatment, cure or prevention of a disease or condition in man; (2) is used outside the body on specimens taken from the body; and (3) is subject to licensure under the PHS Act. Note: In-Vivo means in the body and In-Vitro means in glass (i.e. outside of the body).

Human Drugs (Industry Code 60-66): Human drugs are coded under Industry Codes 60-66. Due to the large volume of drug products, numbers 60 through 66 are reserved for human drugs. Information from the manufacturer or the product label should be used when coding human drug products. Some important points to keep in mind when coding human drugs are listed below.

- The intended use of a product, which is frequently conveyed by the product label, is a very significant factor in determining if a product is a drug. A product is considered to be a drug if the label contains claims that it will prevent or treat a disease or that it will affect the structure or function of the body. For example, wrinkle-removing cream might typically be thought of as a cosmetic (Industry code 53). However, if the label contains anti-aging claims, then the product is coded as a drug because its intended use is to affect the structure or function of the body.
- Product codes for drug products are determined on the basis of the "active" ingredients in the product. An "active" ingredient is the one that causes the product to have the effect that the label claims. If a drug product has multiple active ingredients, its product code is determined on the basis of the first active ingredient listed.
- Normally, the first step in coding human drug products would be to search for the name of the active ingredient. In many cases, this method will provide the Industry Code, Product Class and Product Code, leaving the Subclass and PIC codes for you to select. The Subclass categories are similar to those for Vitamins, Minerals, Proteins, and Unconventional Dietary Specialty products and Antibiotic products. PICs are the same as those used for Antibiotic Products and provide information about the dosage form of the drug product, e.g. prompt release tablets, extended release tablets, prompt release hard gelatin capsules, powders, etc. The label of a product usually provides the information necessary to determine the proper PIC.
- Note that the human drug product codes have not been updated for some time. Use Product Code 66 Y [ ] [ ] 99, for both prescription (Rx) and non-prescription (non-Rx) products that cannot be coded elsewhere. The Product Class code "Y" stands for Exhibit, Other Drug Related Item and can be used for miscellaneous products that you cannot code elsewhere.
- It may not always be obvious that a human drug product is Rx or non-Rx. The label for a prescription drug should bear the symbol "Rx only." The label may have more descriptive statements indicating that the Rx drug is limited to prescription only. Unapproved imported drugs may not have an equivalent statement, as there is no international agreement on what constitutes a Rx drug. It may be considered Rx in the U.S. but Over-the-Counter (OTC) in another country. The strength of the drug also may determine if it is Rx or non-Rx. Filers and inspectors need to rely on the label when determining if a drug is Rx or non-Rx.

Glossary

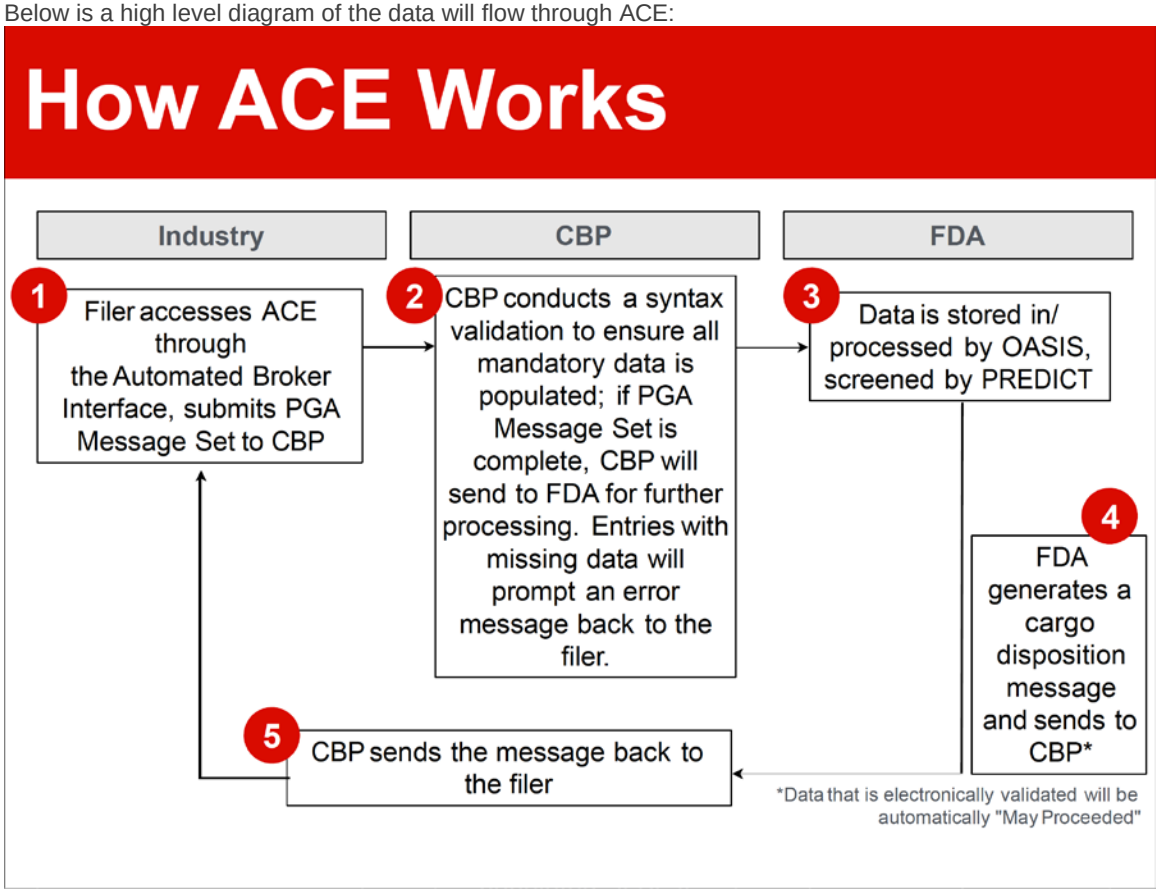
- Drug Products**:** A product is considered to be a drug if it meets any one of the following definitions:
  - articles recognized in the United States Pharmacopoeia (USP), Homeopathic Pharmacopoeia and the National Formulary (NF).
  - articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.
  - articles (other than food) intended to affect the structure or any function of the body of man or other animal.
  - articles used as a component of any such product.
- Rx**:** A human drug product that can only be obtained with a prescription.
- Non-Rx: A human drug product that can be obtained without a prescription.

Appendix C: FDA's Integration to the Automated Commercial Environment (ACE) / International Trade Data System (ITDS)

The Automated Commercial Environment (ACE) International Trade Data System (ITDS) is a single window to facilitate electronic submission of data required for the import and export of goods. ACE replaces the current Automated Commercial System (ACS). CBP, FDA, and 47 Government Agencies are in partnership for this initiative.

By the Executive Order on "Streamlining the Export/Import Process for America's Businesses" of 2014 and the SAFE Port Act of 2006 President Obama mandated that government agencies involved in international trade utilize a "single window" for electronic submission of data for exports/imports to determine admissibility. The deadline for completion and participation in the initiative is December 2016.

Below is a high level diagram of the data will flow through ACE:



Key Terms

- **IWS: (Interoperability Web Services) -** interface for CBP and government agencies to send and receive information and messages
- **PGA Message Set: (Partner Government Agency) Message Set -** harmonized data requirements industry will submit electronically to CBP; CBP will send to respective agency for processing
- **DIS: (Document Image System) -** functionality that will allow industry to upload documents and images (FDA expects to capture all required data via the PGA Message Set)

Changes to Current Business Processes

- Each Center's requirements for cargo admissibility are codified within FDA's Supplemental Guide (allows for standardization across all ports)
- Industry can only submit complete data sets
- OASIS, PREDICT, MARCS ER will function as they do today. Initially, Entry Reviewers will see minimal changes on screen.
- There will be individual Line-Level Release

Appendix D: Violation Code Translations (abbreviated version)

Below are the types of violation codes that may be referenced in a FDA Notice of Action.

Code	Definition
AGR RX	The article appears to be a prescription drug manufactured in the US and offered for import by other than the manufacturer and re-importation does not appear to have been authorized by the Secretary for use in a medical emergency.
AGRINSULIN	The article appears to be composed wholly or partly of insulin manufactured in the US and offered for import by other than the manufacturer and re-importation does not appear to have been authorized by the Secretary for a medical emergency.
BANNED	The article appears to be a banned device.
BIO TOXIN	The article is subject to refusal of admission pursuant to section 801(a)(3) in that it appears to contain a poisonous and deleterious substance which would ordinarily render it injurious to health.
BSE DRUGS	The article is subject to refusal of admission pursuant to Section 801(a)(1) in that it appears to have been prepared, packed or held under insanitary conditions whereby it may have been rendered injurious to health.
CALIBRATED	The article is subject to refusal in that it is calibrated in units not commonly used in the United States.
DANGEROUS	The article appears to be dangerous to health when used in the dosage or manner, or with the frequency or duration, prescribed, recommended, or suggested in the labeling thereof.
DE IMP GMP	The methods used in, or the facilities or controls used for the manufacture, packing, storage or installation do not conform to the requirements under section 520(f).
DE/RX KIT	The article appears to be a combination medical device/prescription drug kit for which the prescription drug component was manufactured in the US, is offered for import by other than the manufacturer, and re-importation does not appear to have been authorized by the Secretary for use in a medical emergency.
DEVICE GMP	The methods, facilities or controls used for the article's manufacture, packing, storage, or installation do not conform with applicable requirements under section 520(f)(1) or a condition prescribed by an order under section 520 (f)(2).
DIRECTIONS	The article appears to lack adequate directions for use.
DIRSEXMPT	The article appears to lack adequate directions for use, and the article does not appear to be exempt from such requirements.
DR QUALITY	The drug appears to be represented as not being recognized in an official compendium and appears its strength differs from or its quality or purity falls below that which it purports or is represented to possess.
DRUG COLOR	The article appears to be a color additive the intended use of which is for the purpose of coloring only, and its packaging and labeling do not conform to regulations issued under section 721.
DRUG GMPS	It appears that the methods used in or the facilities or controls used for manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with current good manufacturing practices.
DRUG NAME	The article appears to be a drug and fails to bear the proprietary or established name and/or name and quantity of each active ingredient.
DV NAME	The article appears to be a device and its labeling fails to bear the proprietary or established name.
DV QUALITY	The article appears to be a device whose quality falls below that which it purports or is represented to possess.
EXPIRED	The product strength differs from, or its purity or quality falls below that which it purports or is represented to possess in that it is past its labeled expiration date.
FAILS STD	The article appears to be a device which is subject to a performance standard established under Section 514 and does not appear to be in all respects in conformity with such standard.
FALSE	The labeling for this article appears to be false or misleading.
FORBIDDEN	The article appears to be forbidden or restricted in sale in the country in which it was produced or from which it was exported.

FRNMFGREG	The foreign manufacturer has not registered as required by section 510(i)(1).
HOLES	The quality of the article falls below that which it purports or is represented to possess, in that the devices contain defects/holes.
INCONSPICU	Information required by the Act to be on the label or labeling does not appear to be conspicuous enough as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.
INVDEVICE	The article is subject to refusal of admission pursuant to Section 801(a)(3) in that it appears to be a device for investigational use for which no exemption has been granted as prescribed by Section 520(g)
N-RX INACT	The article appears to be a nonprescription drug and fails to bear the established name of each inactive ingredient in alphabetical order on the outside container of the retail package.
NO 510(K)	It appears that a notice or other information respecting the device was not provided to the FDA, as required by Section 510(K) and the device was not found to be substantially equivalent to a predicate device.
NO ENGLISH	Required label or labeling appears to not be in English per 21CFR101.15(c)
NO LICENSE	The article appears to be a biological product not manufactured at an establishment holding an unsuspended and unrevoked license issued under the PHSA Biological Products section 351
NO PMA	The article appears to be a class III device without an approved application for premarket approval pursuant to section 515(a)
NO PMA/PDP	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)
NON STD	It appears that the article fails to comply with applicable standards prescribed under section 534.
NOT LISTED	It appears that the drug or device is not included in a list required by Section 510(j), or a notice or other information respecting it was not provided as required by section 510(j) or 510(k).
OMITTED	It appears that a valuable constituent of the article has been in whole or in part omitted from the article.
REDUCED	It appears to be a drug that a substance has been mixed or packed with so as to reduce its strength.
RX DEVICE	The article appears to be a prescription device without a prescription device legend as required by 21 CFR 801.109.
RXCOMPOUND	The labeling fails to bear, at a minimum, the symbol “Rx only”.
STERILITY	The article appears to have been prepared, packed or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health.
SUBSTITUTE	It appears that a substance has been substituted wholly or in part for one or more of the article’s ingredients.
TAMPERING	It appears that the packing does not conform to current good manufacturing practices under 21 CFR 211.132 or tamper-resistant packaging.
TISSUE	This human cell, tissue and cellular and tissue based product is in violation of Section 361 of the Public Health Service Act.
UNAPPROVED	The article appears to be a new drug without an approved new drug application.

Appendix E: Website Links

FDA Oasis Optional Data Elements
http://www.accessdata.fda.gov/scripts/ora/pcb/tutorial/compliance.pdf

FDA Oasis Optional Data Elements Quantity
http://www.accessdata.fda.gov/scripts/ora/pcb/tutorial/information.pdf

Affirmation of Compliance Codes
http://www.fda.gov/downloads/ForIndustry/ImportProgram/UCM349883.pdf

API Importation (Drug has not been withdrawn or removed from the U.S. market for public health reasons - list in Compliance Policy Guidance CPG 460.200)
http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm)

DailyMed
http://dailymed.nlm.nih.gov/dailymed/index.cfm

Device Premarket Notification Review Program
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm

Device FDA Product Code
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm

Device FDA Establishment Registration number or DUNS
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm

Import Alerts
http://www.accessdata.fda.gov/cms_ia/iapublishdate.html

Import For Export
http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074300.pdf

FDA Prior Notice (Tariff Code List)
http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/PriorNoticeofImportedFoods/ucm170031.htm

2009 Final Guidance for Industry on the new electronic Drug Registration and Listing System (eDRLS): http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default.htm

NDC Directory: http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm

DUNS Number request or information – Dun & Bradstreet:
http://www.dnbgov.com/federal_compliance/fda/DUNSrequest/requestGuide.html

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