Human Drug Imports: At a Glance

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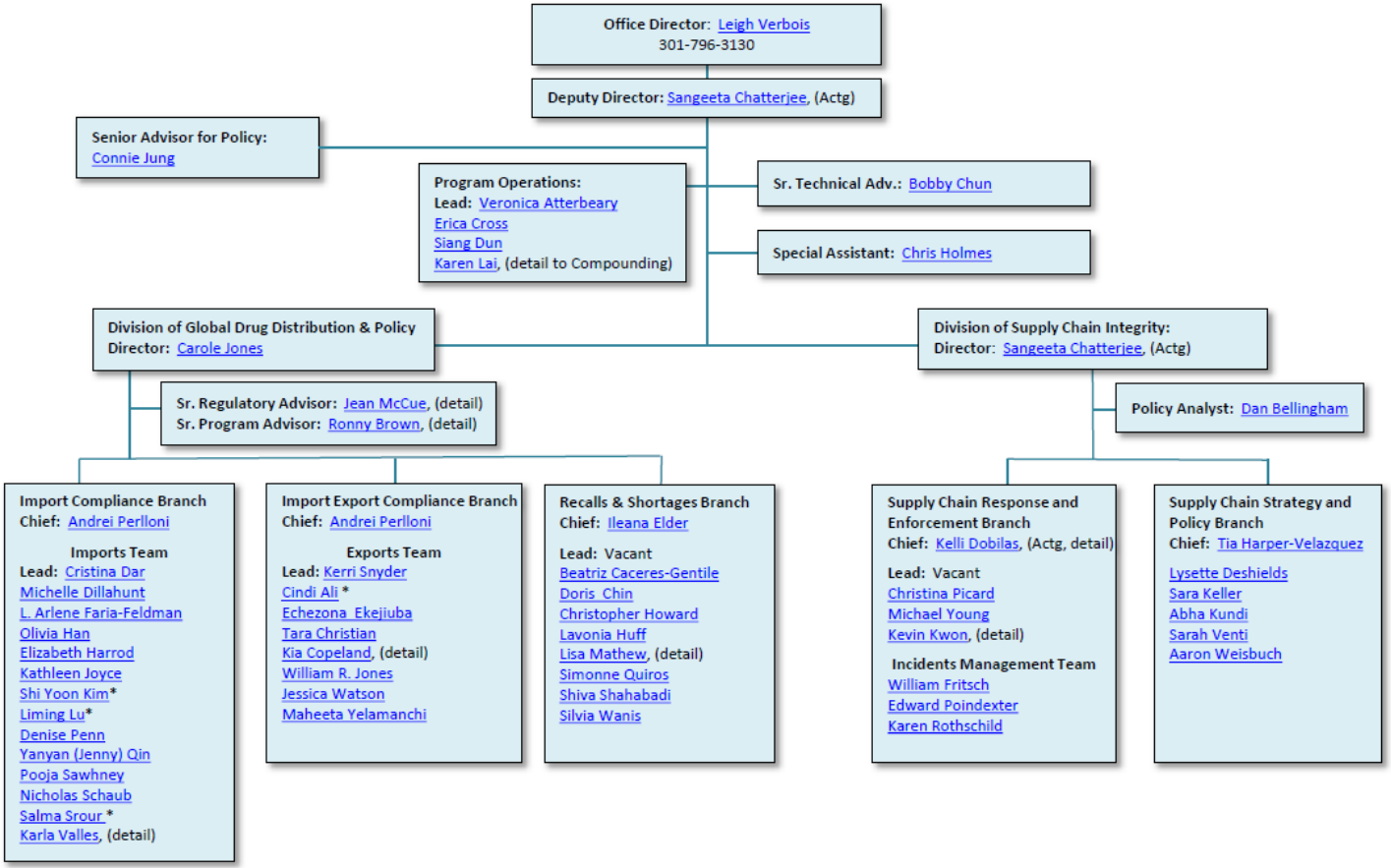
Learning Objectives

- Provide a fresh look of human drug importation requirements
- Clarify importation requirements for different drug types
- Discuss routes of importation of human drug products

CDER OC Office of Drug Security, Integrity, and Response (ODSIR)



The Why

- FDA is responsible for protecting the public health.

  ODSIR's mission is to:

  Protect the integrity of the global supply chain throughout the drug lifecycle to minimize consumer exposure to unsafe, ineffective, and poor quality drugs.

Imports

- Imported drugs must meet the FDA's standards for quality, safety, and effectiveness
- FDA reviews shipments of imported drugs to determine whether they are admissible into the US
- These requirements are verified at the time of importation

Example of Impact

- Working with Custom and Border Protection (CBP), FDA identified hand sanitizers being imported, which are considered over the counter drugs, that contained methanol
- Methanol is a toxic substance
- FDA implemented measures to mitigate the importation of unsafe hand sanitizers to protect the public health

FDA's Regulatory Purview

What is a drug?

Drugs include 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 animals; and articles intended for use as a component of a drug [201(g)(1)].

Drug Importation Authorities

Section 801(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 301(a) prohibits the introduction or delivery for introduction into interstate commerce (***includes importation***) of misbranded, adulterated, and unapproved new drugs.

Under section 801(a) of the Act, an article (drug) is subject to ***refusal*** if it appears from examination or otherwise that:

(1) It has been manufactured, processed, or packed under unsanitary conditions

(2) Forbidden or restricted for sale in the country in which it was produced/exported

(3) Is adulterated, misbranded, or in violation of section 505 of the Act

Drug Importation Authorities—con't

- Adulteration (section 501 of the FD&C Act)
  - CGMP issues
- Misbranding (section 502 of the FD&C Act)
  - Lack of adequate directions for use or evidence of qualification for exemption
- Violation of section 505 of the FD&C Act)
  - New drugs without an application
  - This includes Investigational New Drugs (INDs)

Drug Importation Requirements

Types of Drugs

Prescription and generic medicine

New Drug Application (NDA)

Abbreviated New Drug Application (ANDA)

CDER regulated Biologics License Application (BLA)

Active Pharmaceutical Ingredients (APIs) also known as Bulk Drug Substance

Investigational new drugs (INDs)

Over the counter drugs (OTC) also known as nonprescription medicine

Import Admissibility Requirements

At the time of importation, FDA will verify compliance with the following requirements as applicable:

- Registration and listing
- NDA/ANDA/CDER regulated BLAs
- IND
- Compliance with applicable labeling requirements

Ensure that products/manufacturers are not on import alert

Drug Registration and Listing

Foreign establishments that manufacturer, repack, relabel, or salvage drug products for importation to the US are required to:

- Register with FDA (501(i))
- List all of their commercially distributed drug products with FDA (510(j))

Foreign establishments required to register with FDA must list all known importers in their registration

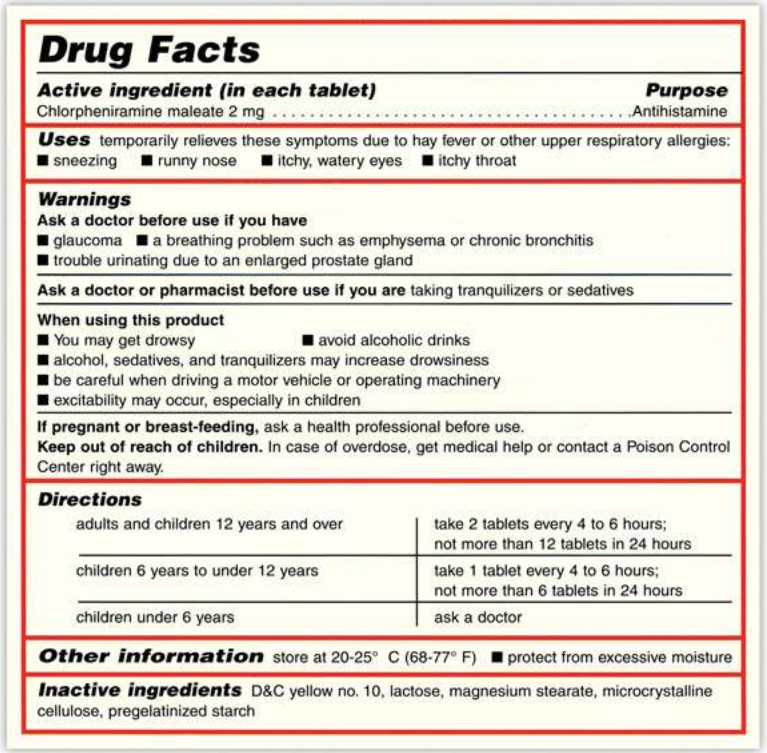
Drug Label Requirements

All drugs offered for importation into the US are subject to labeling requirements: General labeling requirements are found in 21 CFR 201.1-201.328.

- Product labeling should bear all required information in English
- Exception: Label in Spanish for distribution in the Commonwealth of Puerto Rico is authorized under 21 CFR 201.15(c)
- A prescription Drug (503(b)(1)) is required to include the “Rx only” symbol on its label (503(b)(4))

Drug Label Requirements—con't

- OTC Drug Facts label:
- Specific warnings (keep out of reach of children)
- Inactive ingredients
- Active ingredients, including the amount in each dosage unit



Drug Facts

Active ingredient (in each tablet) — **Purpose**
Chlorpheniramine maleate 2 mg ..... Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings
Ask a doctor before use if you have
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis
■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product
■ You may get drowsy ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers may increase drowsiness
■ be careful when driving a motor vehicle or operating machinery
■ excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

Other information store at 20-25° C (68-77° F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

Active Pharmaceutical Ingredients (APIs)

- APIs are considered to be drugs (21 CFR 207.1)
- APIs have to be declared to FDA
- APIs have to comply with the applicable requirements of the finished drug product: Register and List

NDA/ANDA/BLA for the finished drug product in which the API is used

- APIs also have labeling requirements (21 CFR 201.122)

Affirmation of Compliance Codes (AofCs) Qualifiers

- Three-letter codes that can be provided at the time of import to demonstrate compliance and facilitate FDA review of import requirements
- Only mandatory in some instances and are not required for all scenarios
- Submitting voluntary AofCs may expedite initial screening and review
- Submitted through Automated Commercial Environment (ACE)

Affirmation of Compliance Codes (AofCs) Qualifiers

Drugs		
Code	**Affirmation of Compliance**	**Qualifier?**
DA	New Drug Application No. or Abbreviated new Drug Application No. or Therapeutic Biologic Application No.	Y
DLS	Drug Listing Number	Y
ERR	Entry Review Requested	N
FSR	Canadian Foreign Seller Registration Number	Y
IDE	Investigational Device Exemption Number	Y
IND	Investigational New Drug Application Number	Y
LST	Device Listing Number	Y
PLR	Used to identify shipment as a PLAIR import shipment	N
PM#	Device Premarket Number	Y
PRN	Pre-Import Request Number	Y
REG	Drug Registration Number	Y

Not an all inclusive list

Intended Use Codes (IUCs)

- Allows the Agency to know the purpose of the shipments coming into the country
- Determines which A of Cs are needed and which do not have to be provided
- IUCs are different from product intended use:
  - Product intended use is the intended use of the product with the patient
  - Import Intended use is the intended importation route of the product

Routes of Drug Importation

Routes of Importation

- US Good Returned
  - Prescription drugs can only be re-imported into the US by the original manufacturer, examples: Recalled products, overstock, returns
- Import for Export (801(d)(3) of the FD&C Act)
  - Allows for the importation of a product that is unapproved or otherwise does not comply with FDA laws and regulations if it is coming into the US for further processing or incorporated into a product for export and ultimately exported out of the US.

Routes of Importation—con't

Personal Importation Policy (PIP): covers importation of a product not for further sale or distribution into US commerce.

- FDA typically does not object to the personal importation of unapproved drugs that meet the criteria listed in Regulatory Procedures Manual (RPM) Chapter 9, Subchapter 9-2: Coverage of Personal Importations.

Non-clinical R&D Importations

- Non-clinical research an development: Product is not intended for use in humans
- Exempt from registration and listing requirements
- Ensure the quantity is reasonable for the research to be performed
- It is often beneficial to include a statement of intended use (separate from the IUC) when these products are imported into the US

Non-clinical R&D Case Scenario

Drug (includes APIs) intended for use in non-clinical R&D to generate data needed to submit an IND:

- FDA may consider not objecting to its import. To assist FDA in its admissibility review of a drug intended for non- human R&D; helpful to include an intended use statement with the import entry documentation that:

    1. Provides a description of the drug's intended use, including the specific research to be conducted;
    2. Affirms that the quantity offered for import is reasonable for the intended research use; and
    3. Affirms the drug will not be commercially distributed.

PLAIR

Pre-Launch Activities Importation Requests (PLAIR)

- Allows, in certain circumstances, product sponsors anticipating approval of a drug application (NDA, ANDA, BLA) to:
  - import unapproved finished drugs products (FDP) in order to prepare for market launch
  - Submit to CDER-OCPLAIR@fda.hhs.gov
- The amount of drug product imported into the US must match the amount in original PLAIR submission
  - Otherwise, an amended PLAIR should be submitted to CDER-OCPLAIR@fda.hhs.gov for approval

Challenge Question #1

Which of the following statements is NOT true?

A. APIs are considered to be drugs (21 CFR 207.1)

B. APIs have to be declared to the FDA

C. APIs do not have to comply with applicable requirements of the finished dosage drug product.

D. APIs also have labeling requirements (21 CFR 201.22)

Challenge Question #2

Foreign establishments required to register with FDA must list X in their registration.

A. Imported drugs only
B. Imported drugs and known importers
C. Imported drugs and all known importers
D. All known importers only

Resources

- Affirmation of Compliance Codes
- Human Drugs
- Human Drug Imports
- Personal Importation
- Drug Registration and Listing System (DRLS & eDRLS)
- OTC Drug Facts Label

Summary

- FDA will verify compliance with applicable requirements of a drug at the time of importation.
- Before importing a product, identify whether it is a drug and learn the applicable requirements.
- If you are an importer, review the history of the foreign manufacturer to make sure it is not on import alert.

U.S. FOOD & DRUG ADMINISTRATION

Questions?

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