

Drug Imports Exports Compliance





CDER Office of Compliance
Office of Drug Security, Integrity & Recalls
Division of Import Operations & Recalls
Imports Exports Compliance Branch

FDA compliance focal point for imports exports of CDER regulated Human Drugs

cderimportsexports@fda.hhs.gov

Our language

- FFDCFA or FDCA – Federal Food, Drug, and Cosmetic Act (the Act or 21 U.S.C.)
- CFR – Code of Federal Regulations (the Regs or 21 CFR)
- IA – Import Alert
- CPG – Compliance Policy Guide
- On Screen Reviews
- ORA, CFSAN, CDRH, CBER, CVM, CDER

General Drug Imports Requirements

- What is a chemical?
- What is a drug under the FFDCA?
- Recognize various drug imports requirements:
 - Registration and Listing Requirements
 - Labeling
 - Marketing requirements for OTC and Rx Drugs
 - Addressing Adulteration
 - Misbranding & Adequate Directions for Use
 - Importation of Drug Products (finished dosage form) and Active Pharmaceutical Ingredient (API)
 - Diversion of imported APIs
 - Personal Importation Policy (PIP)

Drug Imports

US Imports Drug regulation and inspection at the border dates to the Import Drug Act of 1848

Modern FFDCA dates to 1906 and 1938

Q: When does the drug import process begin?

- A. before regulated products leave the exporting country
- B. once products reach a CBP point of entry
- C. after FDA conducts foreign inspections
- D. as soon as the shipment enters US territory

Mission Statements

- FDA Mission: Successfully assess, manage, mitigate, and to the extent possible, eliminate public health risks that FDA-regulated products may pose to U.S. consumers.
- Center for Drug Evaluation and Research: CDER assures that safe and effective drugs are available to the American people.
- Office of Compliance: To promote and protect public health through strategies and actions that minimize consumer exposure to unsafe, ineffective, and poor quality drugs.
- *Imports Exports Compliance Branch: To promote and protect the public health by ensuring drug importation and exportation adhere to FDA standards of compliance.*

Drug Imports & Exports

- FDA is responsible for assuring the safety and effectiveness of domestic, imported drugs and other products.
- Food, Drug, and Cosmetic Act (FDCA) Section 301(a) prohibits the introduction or delivery for introduction into interstate commerce (*includes importation*) of misbranded, adulterated, and unapproved new drugs.
- Per FDCA 801(a) the FDA may detain and refuse admission of any drug which *appears* violative:

“If it appears from the examination of ... samples or otherwise ... then such article shall be refused admission ...”

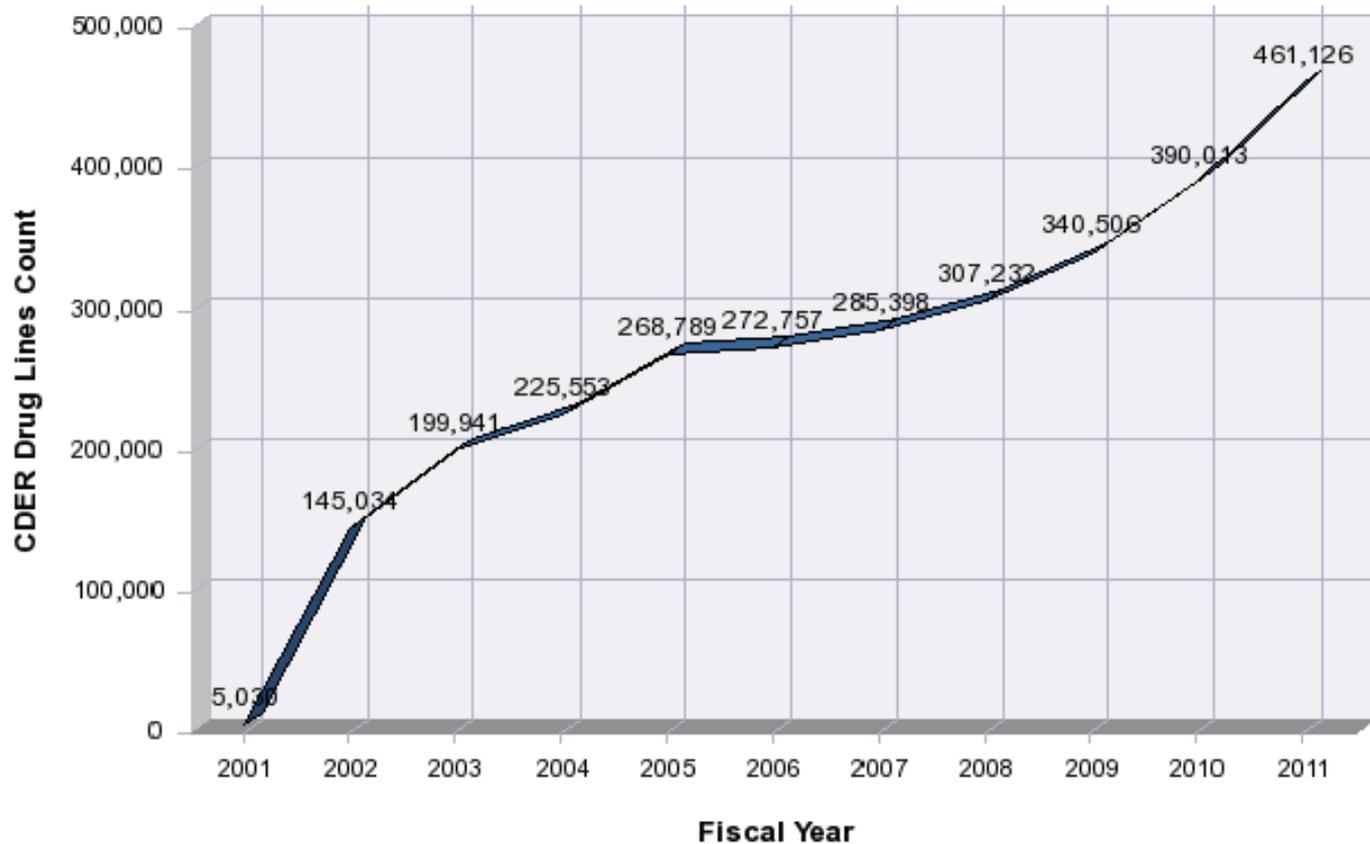
Imported Drugs

Current Information and Issues

- US imports 80% of APIs & 40% of finished drugs
- Drug Shortages, Heparin, DEG, Povidone, K-2, steroid hormones, drug analogs, pro-hormones
- Human Growth Hormone (hGH) and human Chorionic Gonadotropin (hCG) smuggling
- Drug diversion: ketamine/levamisole
- Dietary supplement adulteration with drug ingredients

Ten Years of Drug Imports

CDER Regulated Drug Importation

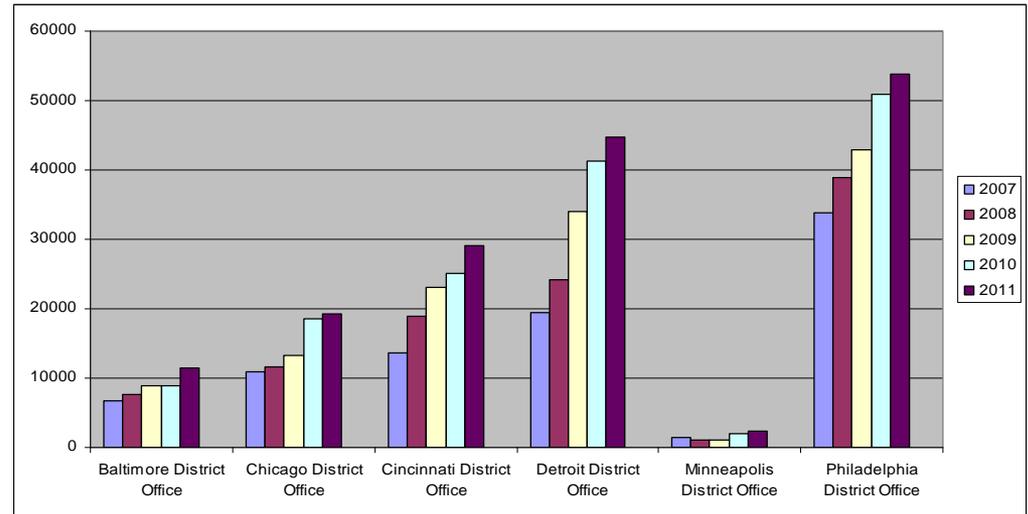


Globalization of Drug Sourcing

- 2006 - over 160 countries, 81% from top 10 Canada, UK, France, **Germany**, India, Mexico, Israel, Italy, China, Japan
- 2007 - over 170 countries, 83% from top 10 Canada, Mexico, India, France, Israel, Germany, UK, Italy, China, Japan
- 2008 - over 170 countries, 84% from top 10 Canada, Mexico, India, France, Israel, Germany, UK, China, Italy, Japan
- 2009 - over 160 countries, 84% from top 10 Canada, India, Mexico, France, Germany, Israel, UK, China, Italy, Ireland
- 2010 - over 160 countries, 82% from top 10 Canada, India, Mexico, Israel, France, Germany, China, UK, Italy, Belgium
- 2011 - over 150 countries, 90% from top 10 Canada, India, Mexico, UK, France, China, **Germany**, Israel, Italy, Belgium

This data does not include products declared of US origin or international mail.

Central Region CDER Drug Imports



Sustained growth of CDER regulated drug entries in all Districts

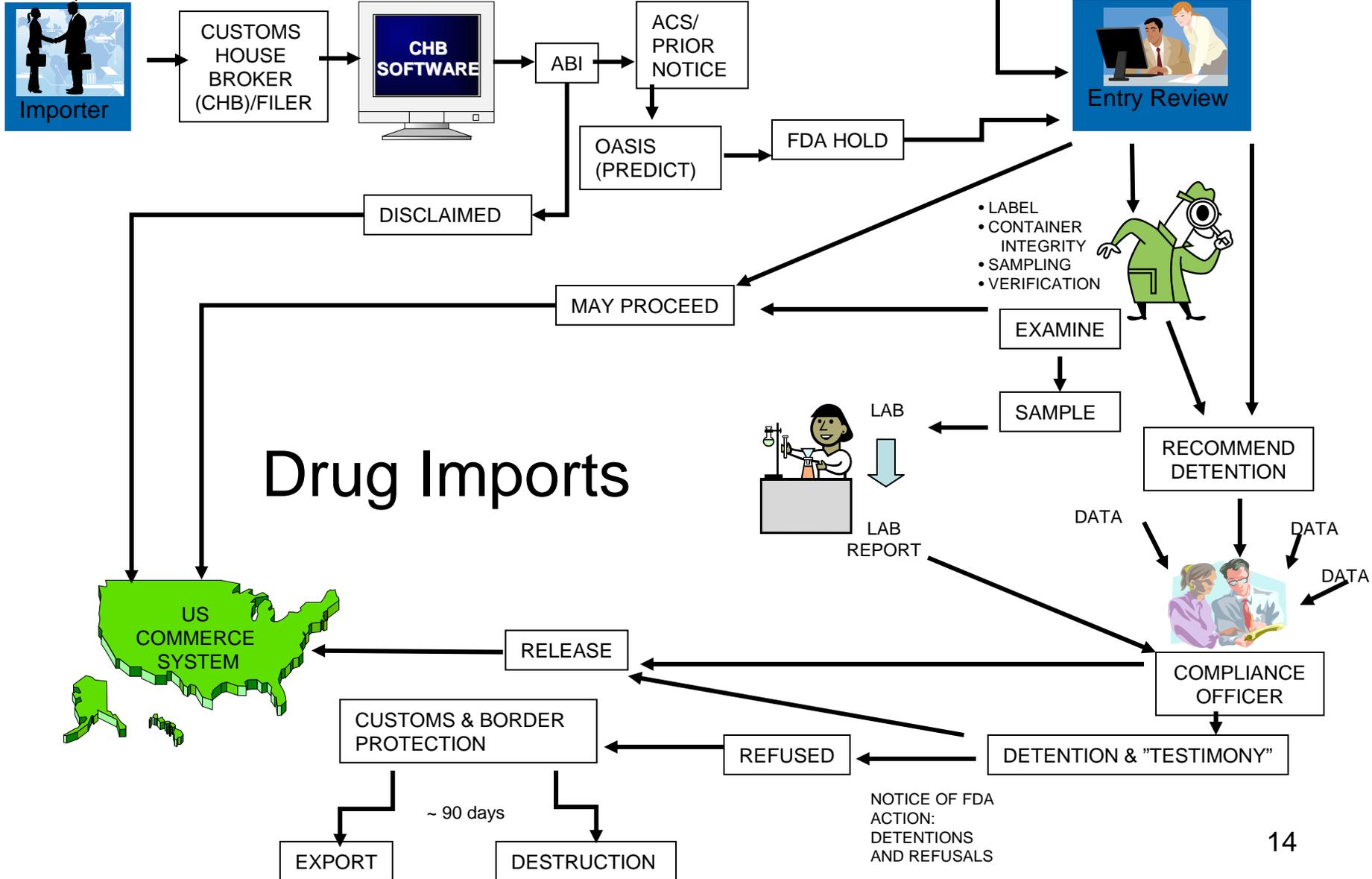
Imports Admissibility

- Administrative Detention and Hearing Process
 - Happens at the District level (see 21 CFR 1.94)
 - Notice of FDA Action
 - 766 reconditioning certain misbranded drugs into compliance
 - Unapproved new drugs may not be brought into compliance see RPM Chapter 9:
 - “Do not permit the relabeling of a drug detained on a new drug charge as a means to bring the item into compliance.”
- Products not brought into compliance are refused
- Refused articles must be destroyed or exported
- If the drug poses a health hazard, FDA and Customs & Border Protection (CBP) may request restricted redelivery.

Drug Imports Entry Review Tools

- Intelligence & our collective Experience
- PREDICT, MARCS-OASIS, Documents, Labels
- Databases (DRLS, DAARTS, EES, eLIST, eDRLS)
- Import Alerts and Assignments
- Division of Import Operations & Policy (DIOP)
- CDER Office of Compliance
 - Imports Exports Compliance Branch
- Other Government Agencies



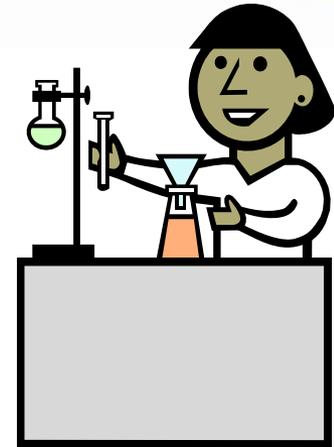


Entry Review Decisions

Five decisions may result from the entry evaluation process:

- (1) may proceed
- (2) request additional information for further evaluation
- (3) refer to Compliance for detention
- (4) field examination
- (5) sample collection.

Chemical or Drug



- Per the FFDCA
 - chemicals can be drugs
 - not all chemicals are drugs

- 21 CFR 201.128, the meaning of “intended uses”
 - Intent is determined by labeling, advertising matter, oral or written statements

- Inherent Use (not defined in the Act or regs)
 - Assert jurisdiction based on inherent nature of the product, its actual use or effects, or a combination of these

- Khat, GHB (gamma hydroxybutyric acid), Procaine, Bath Salts, Dimethyl Sulfoxide (DMSO), Kratom

Definition: “Drug” *[FDCA 201(g)(1)]*

Drug is an article ...

- Intended to diagnose, cure, mitigate, treat or prevent disease in man or other animals
- Intended to affect the structure or any function of the body of man or other animals (other than food)
- Recognized in the United States Pharmacopeia/National Formulary, Homeopathic Pharmacopeia of the United States or any supplement to the said lists
- Intended for use as a component of a drug

Definition: "New Drug" *[FDCA 201(p)]*

- "any drug ... the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience..., as safe and effective (GRAS/E) for use under the conditions prescribed, recommended or suggested in the labeling"
- A "new drug" must be covered by an approved new drug application (NDA/ANDA) to be marketed in the U.S. or by an investigational new drug application (IND) *[FDCA Section 505]*
- Applies to both Rx and OTC drugs

Drug or Device

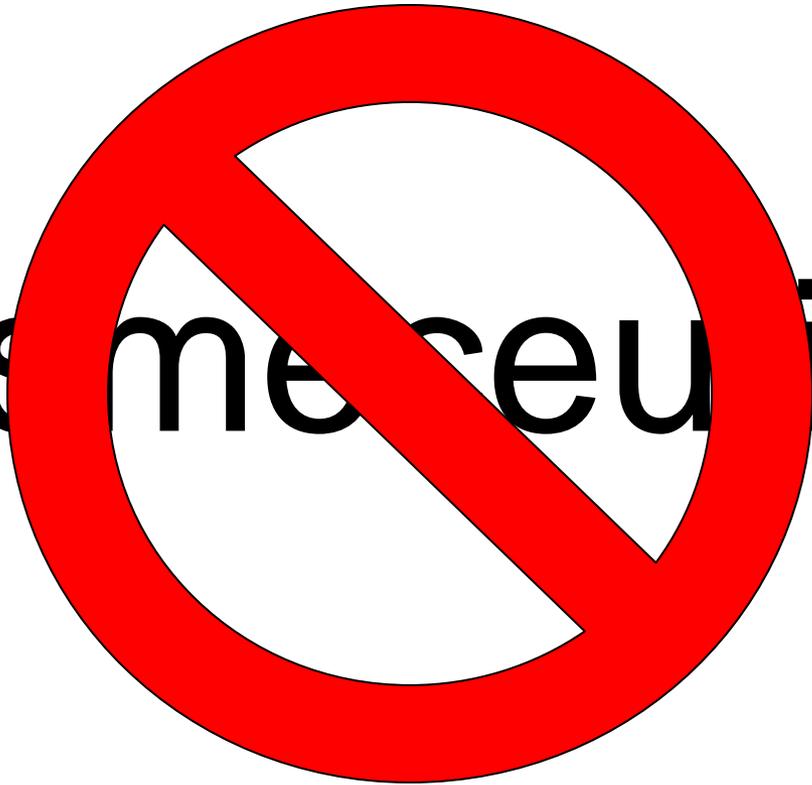
- When a firm submits a device listing it is required to state why the product is not a drug (see FDCA 510(j)(1))
- Combination products (21 CFR 3.2(e))
- Convenience kits containing both are required to meet both regulatory requirements

Drug or Cosmetic

- A cosmetic is a drug –
Example, “cosmetic” with anti-aging, wrinkle, scar claims
- Both drug and cosmetic – antimicrobial soap and antiperspirant/deodorant
 - These products must meet both the drug and cosmetic regulations.
- Cosmeceuticals?

HYBRID Laws & Regulation?

cosmeceutical



Drug or Dietary Supplement

- Dietary supplements must meet definition found at FDCA Section 201(ff)(1)
- Cannot be a dietary supplement if it is not ingested or when it is intended to treat, cure, prevent, mitigate disease
- Products that otherwise can be dietary supplements are drugs if they contain a drug that is the subject of an approval, i.e., steroid
- Nutraceuticals?

HYBRID Laws & Regulation?

nutraceutical



Tainted Dietary Supplements

Current surveillance resulted in:

- Weight Loss – 72 products found with various APIs
 - Controlled substances or banned substances
- Erectile Dysfunction – over 40 products found with APIs
 - Drugs known to have serious side effects
- Other types of contaminated dietary supplements:
cholesterol lowering, diabetes, bodybuilding, sleep aids

Sibutramine: controlled substance and API in Meridia

Bumetanide: a potent diuretic available by prescription only

Fluoxetine: an antidepressant available by prescription only

Rimonabant: not approved for marketing in the U.S.

Cetilistat – an experimental obesity drug not approved for marketing in the U.S.

Weight Loss Products



“Diet” & “Gentlemen” Nutritional Supplements



Body Building

- American Cellular Labs
- Violative products
 - TREN-Xtreme, MASS-Xtreme, Estro Xtreme, AH-89-Xtreme, HMG Xtreme, MMA-3 Xtreme, VNS-9 Xtreme, TT-40-Xtreme
- Unapproved New Drugs
 - Synthetic steroids
 - Some products claim to affect the structure or function of the body
 - Labeling can make the product an unapproved new drug.



Lifestyle Drugs

- Dietary Supplement
- Nutrition Facts
- Ingredients
- Instructions
- Websites w/ structure function claims
- Certificate Of Analysis
- Prior Notice information
- Undeclared drug analog



Legal Violations

A Dietary Supplement with structure function claims is regulated as an unapproved new drug if:

- the product contains an article approved as a drug

and/or

- the product contains a non-dietary drug ingredient

Note: structure/function claims can only be made for dietary ingredients, not chemicals that do not meet the definition of dietary ingredient.

CDER New Drug Approval (NDA/ANDA)

- Product, firm, manufacturer, label specific
- Firm submits data on safety and efficacy
- FDA evaluates data, approves or does not approve the drug
- Every firm must seek FDA approval for any drug product requiring FDA approval

Approved new drug must be:

1. Manufactured, packaged, or labeled at a facility covered in the application using the formulation and process approved
2. Manufactured using an API supplied by a manufacturer covered in the application

Definition: Prescription (Rx) drugs

[FDCA 503(b)(1)]

Drugs that cannot be used safely without medical supervision.

– Examples?

- Injectable* drugs
- Drugs to treat serious conditions like heart disease, cancer, or fertility issues

*Generally, injectable drugs are Rx, but insulin is not Rx in every state.

Definition: Over-The-Counter (OTC) drug

- All other drugs that can be used safely without medical supervision

Examples:

- Medications for fever such as aspirin and acetaminophen
 - Some preparations for common cold or allergies
 - Antacids
 - Some first aid antibiotics
- If a drug can be marketed OTC, it must be marketed OTC. Cannot market it as Rx drug.

OTC Drugs

- Most OTC drugs are not covered by NDAs
- Large number of OTC drugs on the market in 1972 did not have FDA approval
- Agency decided to have a class-by-class review for OTC drugs instead of NDAs
- Final rules (OTC monographs) in effect 21 CFR Parts 331 through 358
- Negative monographs at 21 CFR 310
 - Timed-release drugs require new drug application approval (see 21 CFR 310.502(a)(14))

OTC Drugs

- Where there is a final monograph, OTC drug must meet the final monograph including labeling and formulation.
- Drug must be manufactured under cGMPs.
- Some drugs switched from Rx to OTC still require NDA (ibuprofen, Advil).
- Tamper-evident packaging & labeling

LABELING

- OTC drug products must also comply with all other FDCA labeling requirements.

Drug Label Requirements

Per FDCA, all drugs must bear:

- 502(b) – The name & place of manufacturer, packer, or distributor (also see 21 CFR 201.1)
- 502(b)(2) – Accurate statement of the quantity of contents
- 502(c) – Must be understandable, must be in English (also see 21 CFR 201.15)
- 502(e) – Established name and quantity of each active ingredient (also see 21 CFR 201.10)

Drug Label Requirements

- Adequate directions for use (21 CFR 201.5)
- 502(f)(1) – Misbranding and exemption from charge
 - Drug products, that is, finished dosage form Rx drugs are exempt when they meet all labeling conditions at 21 CFR 201.100
 - APIs are exempt from misbranding when they meet certain labeling requirements

Active Pharmaceutical Ingredient (API)

[21 CFR 207.3(a)(4)] a.k.a. bulk drug substance

"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...**"

"term does not include intermediates used in the synthesis of such substance"

- Lyophilized drugs such as hGH and hCG are finished drugs, not APIs – Require NDA approval

Registration: Domestic & Foreign

- **FDCA 510(b), (i) – Registration Requirements**
 - Manufacturers: API & finished drug products
 - Repackers and relabelers
 - Control laboratories: registration only
 - Domestic manufactures that pack/repack, label/relabel, etc. drugs under the Import for Export (IFE) requirements

- **NO ESTABLISHMENT REGISTRATION?**
 - Drug is misbranded under FDCA 502(o)

Foreign Firm Registration & Drug Listing [FDCA Sec. 510 & 21 CFR 207]

All foreign firms that manufacture, prepare, propagate, compound, or process a drug imported or offered for import into the U.S. shall, through electronic means ...

- Register the name and place of business
- Designate a U.S. Agent
- Provide names of each known importer & person who imports or offers for import
- List all drug products imported or offered for import into the U.S.

Drug Listing: Requirements

- FDCA 510(j) – Drug Listing
- NO or INADEQUATE DRUG LISTING?
 - Drug is misbranded under 502(o) and subject to refusal under section 801(a)(3).
- NDC Numbers
 - FDA requests but does not require NDC appear on the product label or labeling
 - If NDC appears on the label it must comply with regulation at 21 CFR 207.35 (b)(3)

Registration & Listing

- Listed products: assigned National Drug Code number (NDC #)
- NDC # format identifies the following:
 - Labeler code: manufacturer or distributor
 - Product code: drug formulation
 - Package code: trade package size and type
- Registration or Listing does not indicate FDA's approval of firm or products [21 CFR 207.39]

Registration: Exemptions

- Pharmacies that operate under applicable local laws that do not manufacture or process drugs for sale (21 CFR 207.10(a))
- Hospitals, clinics, and public health agencies that operate with any applicable laws regulating the practice of medicine and pharmacy (21 CFR 207.10(b))
- Practitioners who are licensed by law to prescribe or administer drugs (21 CFR 207.10(c))
- Persons who manufacture or process drugs not for sale but solely for use in research, teaching, or chemical analysis (21 CFR 207.10(d))
- Manufacturers of harmless inactive ingredients (21 CFR 207.10(e))

Listing: Exemptions

- Component of a drug (e.g. ingredients or non-API intermediates used to synthesize APIs)
 - Heparin is not exempt
- Drugs not for importation into U.S. (into FTZ)
 - Component used to manufacture per 801(d)(3)
- Investigational New Drug (IND) [21 CFR 312]
- Research for own study only and not for research in humans. Not exempt when the importer is different from the researcher.

Affirmations of Compliance

AofC: NDA, NDC, DLS, REG, CFR, UFC, etc.

Test Question:

I provided a valid NDC number so the drug is approved:

(T)rue

(F)alse

I provided a valid NDC number therefore:

- (a) The firm is adequately registered and drug is listed
- (b) The drug can be marketed
- (c) The drug is an investigational drug

Affirmations of Compliance

I provided a valid firm registration number
therefore the drug is listed:

(T)rue

(F)alse

The active pharmaceutical ingredient (API) has a
different listing from the finished dosage form
listing number:

(T)rue

(F)alse

Marketing Requirements: DESI

- Drug Efficacy Study and Implementation review per FDCA Drug Amendments of 1962 to assess effectiveness of drugs previously found to be safe under the Act
- *DESI drugs* are drugs that were the subject of pre-1962 (safety only) NDAs and drugs that are identical, related, and similar to such drugs [21 CFR 310.6]

DESI

- CPG 440.100 describes how FDA intends to exercise its enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing see:

<http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074382.htm>

- Although theoretically possible we are not aware of a known "grandfathered drug"
- APIs do not qualify for consideration

Imported Drugs

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

- (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

801(a)(3)

- Adulteration (FFDCA 501)
 - GMP issues
- Misbranding (FFDCA 502)
 - Lack of adequate directions for use or evidence of qualification for exemption
- Violation of 505
 - new drugs without an application
 - this includes INDs

Adequate Directions for Use - Misbranding

[502(f)(1) & 21 CFR 201.5]

- Definition: “directions under which a layman can use the drug safely and for the purposes for which it is intended”
- 21 CFR 201.128 defines “intended uses”, includes objective intent determined by the expression or circumstances surrounding distribution
- All drugs (including APIs) must bear “adequate directions for use” or qualify to meet one of the **exemptions** (If not, then misbranded *[502(f)(1)]*)
- **OTC** finished drug products meet this requirement if they meet a final OTC monograph

Intended Use

- How many intended uses can I claim for my imported drug?
- How many labels can my imported drug have?
- Explanation or statement of intended use, intended use letters, etc.

API – Active Pharmaceutical Ingredient

Drug Product – a finished dosage form Rx or
OTC drug

Misbranding Exemptions

[502(f)(1) & 21 CFR 201.5]

- *21 CFR 201.120 & 201.122 API intended for pharmacy compounding (not finished product)*
- *21 CFR 201.125: Drug product intended for use in **teaching, law enforcement, research, and analysis and not for use in humans***
- *21 CFR 312.160: A new drug for investigational use with laboratory research animals or in-vitro testing, not for use in humans*

API/bulk drug labeling and 502(f)(1) Misbranding Exemptions

Before your firm can label an API your firm must qualify to label the API.

Your firm may qualify if you can demonstrate the intended finished product is not a new drug.

21 CFR 201.122

- *201.122(a)*: API intended for use in a product **approved** in NDA, ANDA, or supplement
- *201.122(b)*: API intended for use in product **subject** to an IND
- *201.122(c)*: API intended for use in product subject to a **pending/near** NDA or ANDA or supplement approval

API Exemptions from Misbranding

[21 CFR 201.122(a)]

- Intended for use in a product **approved** in a NDA or ANDA
- Manufactured by the firm **approved** in the new drug application
- Intended for use in **approved** prescription (Rx) and/or over-the-counter (OTC) drugs

API/Bulk Drug Exemptions

[21 CFR 201.122(a)]

Labeling must have the statement:

- “Caution: for manufacturing, processing, or repacking”
- “Rx only” – if in all dosage forms in which the bulk drug may be used is subject to a human prescription *[503(b)(1)]*

API/Bulk Drug Exemptions from Misbranding cont... *[21 CFR 201.122(a)]*

Useful Information upon entry*:

- API name and NDC number
- Name and address of the API manufacturer
- Number of approved NDA/ANDA or supplement
- Intended finished dosage drug product name and NDC number

* Useful Information that may demonstrate applicability of an exemption. Alternative information may also suffice.

API/Bulk Drug Exemptions

Summary *[21 CFR 201.122(a)]*

- API must be labeled per *21 CFR 201.122*
- Intended finished product must be covered by **approved** application or supplement
- API must be from a supplier **approved** in the application/supplement

API/Bulk Drug for Use in Human Clinical Studies

(a.k.a. IND) *[21 CFR 201.122(b)]*

- Must be covered by an active IND
- Must be going to person(s) authorized in IND
- Labeling must bear:
 “Caution: for manufacturing, processing, or repacking in the preparation of a new drug or new animal drug limited by federal law to investigational use”
- Drugs for clinical studies may not be used for manufacturing (one label, one intended use).

API/Bulk Drug for Use in CDER Human Clinical Studies (IND) *[21 CFR 201.122(b)]*

Useful Information:

- Active IND number
- Sponsor's name and address
- Investigator/Researcher
- Drug Name in the IND

Question: Was product shipped after the 30th day since the IND was submitted to CDER for Review?

API/Bulk Drug for Pending/Near CDER NDA/ANDA (Rx & OTC) [21 CFR 201.122(c)]

- Intended for use in a product subject to a **pending/near** NDA, ANDA, or supplement approval
- Manufactured by the supplier included in **pending/near** NDA, ANDA, or supplement approval
- Applies to both prescription (Rx) and over-the-counter (OTC) drugs subject to an approval

API/Bulk Drug for Pending/Near NDA/ANDA

(Rx & OTC) *[21 CFR 201.122(c)]*

Labeling must have the statement:

- “Caution: for manufacturing, processing, or repacking”
- “Rx only” – if in all dosage forms in which the bulk drug may be used is subject to a human prescription *[503(b)(1)]*

API/Bulk Drug for Pending/Near NDA/ANDA(Rx & OTC) [21 CFR 201.122(c)]

Useful Information:

- API product name and NDC number
- Name and address of the API manufacturer
- Pending NDA/ANDA number or supplement
- Finished dosage drug product name and NDC number (if applicable)
- Written commitment that products manufactured with API will not be introduced in commercial distribution until approved

API/Bulk Drug for Pending/Near NDA/ANDA (Rx & OTC) Summary [21 CFR 201.122(c)]

- API must be labeled per *21 CFR 201.122*
- Finished product must be covered by a pending application or supplement
- API must be from a supplier in the pending application/supplement

Supplements & Pending Application

- NDA/ANDA sponsors must ensure with CDER reviewers reason is inputted in the comments folder why application or supplement is pending
- If no reason, then we reserve the authority to assume product cannot be released due to safety and efficacy reasons
 - Major reason for entries being detained
- Foreign OAI Inspections: Entry is not released

OAI: Official Action Indicated (gross CGMP violations)

CGMP: Current Good Manufacturing Practices (21 CFR 210 & 211)

Useful Information

(API Information not in EES)

Useful Information:

1. APIs included in original or initial application:
 - Copy of the documents from original submission showing the supplier of the API (e.g. CMC information with drug substance information)
 - Explain any discrepancies (e.g. change in name or address)
 - FDA Approval Letter

2. APIs included in a supplement:
 - Copy of the official FDA letter approving the supplement and covering the API supplier
 - Explain any discrepancies (e.g. change in name or address)

API for Pre-Submission Batches

[21 CFR 201.122]

Application Pre-Submission Batches

- Drug used to conduct the studies needed to generate data required to submit an application or supplement
- FDA may exercise enforcement discretion

Useful Information to submit upon importation:

- Explanation of API intended use
 - Example: Bioequivalence and/or bioavailability batches.

APIs for Pre-Submission Batches

cont ... [21 CFR 201.122]

Useful Information – Cont.:

- API name and NDC #
- Name and address of the API manufacturer
- Name and address of U.S. consignee
- Must be labeled as per *21 CFR 201.122*
- For supplements - may include NDA/ANDA number to be supplemented and NDC # of finished product

Submit requests to cderimportsexports@fda.hhs.gov

Drugs for teaching, law, research enforcement & analysis [21 CFR 201.125]

- Includes Rx and OTC drug products
- Drug is 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.
- 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.

Drugs for Investigational Use In Laboratory Animals/In-vitro [21 CFR 312.160]

- To conduct R&D work prior to the submission of an IND in animal studies or in-vitro testing
- Must comply with all the requirements under 21 *CFR 312.160*.
- CDER Regulated drug must be labeled:

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

Import Requirements of Investigational New Drug (IND) product

- Imported drug complies with 21 CFR 312.110(a)
- Subject to an IND under 21 CFR 312.40.
 - IND is Active
- Labeling complies with 21 CFR 312.6
 - “Caution: New Drug – Limited by Federal (or United States) law to investigational use”
- It is consigned to an authorized person

API to make Rx drugs

Not Subject to Application Requirement

- Labeling (Must State):
 - “Caution: For manufacturing, processing, or repacking”
 - “Rx only”
- Examples: Animal/Clinical Studies or Bioequivalence Study
- Useful Information to provide upon importation:
 - Name and NDC # of product to be manufactured with the API
 - A statement justifying why an approval is not required for the finished drug product
 - API label content demonstrating compliance with *21 CFR 201.122*

API for OTC Drugs: Pending & Final Monographs

Labeling (Must State):

- “Caution: for manufacturing, processing, or repacking”
- Useful Information to provide upon importation:
 - Name and NDC # of product to be manufactured with the API
 - A statement justifying why an approval is not required for the finished drug product
 - API label content demonstrating compliance with *21 CFR 201.122*

API Imported for Pharmacy Compounding under 503A

- Can compound from an API if:
 - Complies with USP/NF monograph
 - Drug substances are components of FDA approved drugs
 - Bulk drug substances are accompanied by valid certificates of analysis
- Should be declared for Pharmacy Compounding
 - Labeling complies with 21 CFR 201.120 and 201.122

API for Pharmacy Compounding Under the CPG

- May not compound if:
 - Drug products were withdrawn or removed from the market for safety reasons.
 - Bulk active ingredients are not components of FDA approved drugs.
 - Drug substances are made in an unregistered facility.
 - Drug components do not meet official compendial requirements.

API for Human Drug Compounding

- *Importer makes a commitment that API will be used only for compounding human drugs.*
- *Importer also makes a commitment that the API will not be used to manufacture drugs.*
- *Warning: Many Compounding Incidents*

Imported API Summary

API may be exempt from misbranding if:

- meet certain labeling requirements
- are not used to manufacture a finished drug that is an unapproved new drug*
- are manufactured by a supplier approved in the new drug application/supplement or included in a pending application/supplement

* Exempted by regulations or granted enforcement discretion

APIs - Adequate Directions for Use Summary

APIs may be imported to manufacture...

- Prescription (Rx) and over-the-counter (OTC) drugs subject to approved or pending applications or supplements
- Rx drugs not currently subject to application requirements
- OTC drugs subject to pending and final OTC monographs

API – exemptions from misbranding

APIs may be imported...

- To manufacture investigational drugs under IND
- For investigational use in laboratory research animals or in-vitro testing
- For teaching, law enforcement, research, and analysis
- For human pharmacy compounding
- To manufacture pre-submission batches

PLAIR

(Pre-Launch Activities Importation Request)

- FDA's policy to exercise enforcement discretion on the importation of a limited amount of an unapproved finished dosage form drug product in preparation for the market launch based upon anticipated approval
- Drug product may require minimal further processing such as final packaging and/or labeling
- Drug Product may be in final packaged form
- CDER regulated NDA, ANDA or BLA
- Does not apply to bulk ingredients or pending supplements.
- Draft Guidance for Industry (pending)

PLAIR

Background:

- Section 505(a) of the FD&C Act prohibits the introduction of any new drug into interstate commerce unless there is an approved application filed for that drug.
- FDA may exercise enforcement discretion to permit the introduction into interstate commerce of certain unapproved finished dosage form drug products.
- Firm(s) not following the PLAIR procedures will be subject to normal entry procedures.

Where to submit a PLAIR and how to obtain PLAIR information

- A PLAIR can be submitted by email on a PDF compatible format to CDER-OC-PLAIR@fda.hhs.gov mailbox only. This mailbox is also used to provide PLAIR information upon request.

What should be included in a PLAIR?

- Drug product name (complete product description)
- Application number
- Name of CDER's application project manager of the pending application
- NDC (National Drug Code) – if assigned
- Name, address, registration #, telephone # of the foreign drug product manufacturer; US consignee; warehouse or distribution facility owned or under contract with the applicant
- A letter signed by an authorized representative of the applicant certifying various conditions.

When should a PLAIR be submitted?

- **NDA** –no more than 60 days before the user fee goal date for completion of the review of the pending application for approval
- **ANDA**- no more than 60 days prior to expected approval

What happens after a PLAIR is submitted?

- Receipt confirmation is issued to the applicant
- CDER IECB reviews the PLAIR submission
- Check GMP status of foreign manufacturer
- Follow-up with OND for NDAs and BLAs or OGD for ANDAs for any CMC deficiency

The overall review process for the PLAIR can take up to two weeks.

CDER Office of Compliance may exercise enforcement discretion to either:

- **Grant the PLAIR** – CDER notifies the firm by email with instructions to follow.
 - A copy of granted PLAIR is communicated to ORA/DIO. The firm then provides DIO in advance with the import entry number.

Note: the firm must be registered per 510(i) but drug listing per Sec. 510(j) is not a requirement until the drug product has received approval and is ready for commercial distribution.

- **Deny the PLAIR** – due to one or more of the following reasons:
 - Manufacturer(s) are not in compliance with CGMPs
 - Application deficiencies
 - PLAIR is too premature

When a PLAIR is denied, the firm does not need to resubmit the PLAIR but may follow

up within 30-45 days of submission.

Who are the main contacts?

CDER Contacts: Marybet Lopez and Michelle Dillahunt
CDER-OC-PLAIR@fda.hhs.gov

ORA/DIOP Contact: Stella Notzon
DIOPPLAIR@fda.hhs.gov

801(d)(1) & PDMA

- Drug products subject to FDCA 503(b) may be re-imported only by the original manufacturer (no exemptions)
- Definition of Manufacturer for this purpose is restricted to the person who performs all of the following operations (see 21 CFR 201.1):
 - Mixing, Granulating, Milling, Molding, Lyophilizing, Tableting, Encapsulating, Coating, Sterilizing, and Filling sterile, aerosol, or gaseous drugs into dispensing containers

Import for Export (IFE) [801(d)(3)]

- Section 322 of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Public Law 107-188
- Signed into law on June 12, 2002, and amended section 801(d)(3) of the FDCA.
- Allows importation of violative articles of drug, i.e., misbranded, adulterated, and unapproved, if the importer provides certain information to FDA at the time of the initial importation into the United States.

Import for Export (IFE) [801(d)(3)]

- Provided importer affirms in writing that imported drugs will be further processed into products to be exported by the initial owner or consignee in accordance with section 801(e) or section 802 of the Act.
- FDA must be provided with certain information:
 - Written statement article (finished dosage form or API) is to be further processed, and the resultant manufacture, processor, packer, distributor or any entity that had possession of the article
 - CoA to identify the article
 - Records when requested

Import for Export (IFE) [801(d)(3)]

- Must execute a bond for any liquidated damages
- Must maintain records of use and/or destruction
- Must destroy any article not used in production

- Article can be refused admission if credible evidence that it is not intended to be further processed
- Prohibited Acts [301(w)]: Exempts exportation
 - False information and statement
 - Introduction into interstate commerce any article (including finished)
 - Not submitting and maintaining records and COA

Transport and Exportation (T&E)

- Products are transported through the U.S. to be exported.
- Possible issues with T&E
 - Large shipment of “Cosmetics” from Saudi Arabia to JFK to Miami to be exported to Haiti
 - No documentation that a previous large shipment was exported.
 - Customs found second shipment contains Rx steroids
 - Products seized

Foreign Trade Zone (FTZ)

- CBP's designation to exempt from payment of duties, taxes, bonds. Considered by CBP to be outside U.S.
- Articles not offered for consumption, thus not considered "imported or offered for import".
- If in FTZ, subject to FDA laws since considered within the "territory" of the U.S.
- 801 does not apply until article is out of FTZ
- Introducing unapproved new drugs into FTZ violates new drugs [505(a)] and prohibited [301(d)]
- Can bring into FTZ articles of drug (bulk or finished) pending approval

Procedures for Importation

- Drug Importation Procedures are found in Chapter 9 of the Regulatory Procedures Manual (RPM)
- Personal Importation Policy (PIP) is covered in Chapter 9-2.
 - Policy gives guidance factors concerning the importation of drugs by individuals

Exporting Drugs [FDCA 801]

Criteria to legally export drugs:

- (A) meet the specifications of the foreign purchaser;
- (B) not be in conflict with the laws of the country to which they are intended for export;
- (C) be labeled on the outside of the shipping package that they are intended for export; and
- (D) not be sold or offered for sale in U.S. domestic commerce

Exporting Drugs [FDCA 801(e), 802]

- Legally marketed articles of drug in the U.S. have no exportation restrictions
- Articles manufactured specifically for export only may be exported & cannot be marketed in the U.S. [801(e)(1)(D)]
- Articles manufactured specifically for U.S. found to be adulterated, misbranded, or unapproved cannot be exported
- Must keep records (21 CFR 1.101)*

Export Certificates

- FDA issues export certificates
- CDER issues CDER regulated drug export certification per FDCA 801(e)(4)
- \$175 for the first certificate for product exported from US
- Valid for 2 years
- Information? Please contact us at:
cderexportcertificateprogram@fda.hhs.gov

DRUG Import Alerts & Bulletins

- 55-03: Detention Without Physical Examination of Different Forms of Heparin and Heparin-Related Products for CGMP Issues
- 55-04: Gelatin with potentially hazardous microbiological contamination
- 61-07: Domperidone
- 62-05: Sterile drugs from facilities not inspected by FDA
- 66-38: Skin Care Products Labeled as Anti-Aging Creams
- 66-40: Drugs manufactured in violation of GMPs
- 66-41: Unapproved New Drugs
- 66-57: Unapproved Rx drugs
- 66-66: Misbranded APIs
- 66-71: HGH
- 66-72: Unapproved/misbranded drugs- CDER initiative on Rx drugs marketed w/o approval
- 99-34: Drug and Device Firms without a valid drug or medical device firm registration

End



- Thank you!
- Email questions to:
cderimportsexports@fda.hhs.gov