CDER Office of Compliance

Office of Drug Security, Integrity & Recalls

Division of Import Operations & Recalls

Imports Exports Compliance Branch (IECB)

FDA compliance focal point for imports & exports of CDER regulated drugs

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IECB Mission: To promote and protect the public health by ensuring drug importation and exportation adhere to FDA standards of compliance.

Drug Imports in General

Importing drug products (finished dosage form) and drugs in bulk packages (e.g. active pharmaceutical ingredient or API)

Regulatory language

- Federal Food Drug and Cosmetic Act FFDCA, FDCA, or the Act
- Code of Federal Regulations 21 CFR

Recognize important drug imports requirements

- Registration and Listing
- Labeling
- Adulteration
- Misbranding & Adequate Directions for Use

Drug Imports

DOCUMENT REQUEST/INFORMATION

CUSTOMS HOUSE BROKER (CHB)/FILER

ABI

ACS/ PRIOR NOTICE

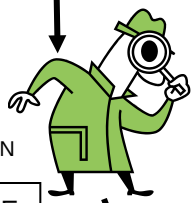
MARCS Imports OASIS (PREDICT)

FDA HOLD

DISCLAIMED

DATA DATA DATA

• LABEL
• CONTAINER INTEGRITY
• SAMPLING
• VERIFICATION



MAY PROCEED

EXAMINE

SAMPLE

LAB

LAB REPORT

RECOMMEND DETENTION

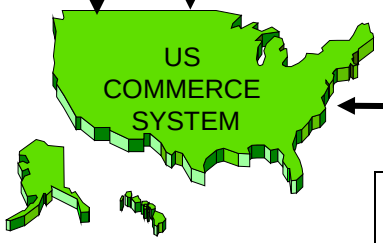
DATA DATA DATA

COMPLIANCE OFFICER

DETENTION & "TESTIMONY"

REFUSED

RELEASE



CUSTOMS & BORDER PROTECTION

~ 90 days

EXPORT

DESTRUCTION

NOTICE OF FDA ACTION: DETENTIONS AND REFUSALS

Imports Admissibility Decision

- Administrative Detention and Hearing Process
  - District review (see *21 CFR 1.94*)
  - Notice of FDA Action
  - 766 reconditioning certain misbranded drugs
  - Unapproved new drugs may not be brought into compliance see Chapter 9 of the Regulatory Procedures Manual (RPM)
- Products not brought into compliance are refused
- Refused articles must be exported or destroyed
- If the drug poses a health hazard, FDA may place restriction

Entry Review Decisions

Five decisions may result from the imports entry review process*

(1) may proceed (not Automatic)
(2) request additional information for further evaluation
(3) refer to District Compliance Branch
(4) field examination
(5) sample collection

*District Offices often work with FDA Headquarters during the review

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

Definition: Prescription (Rx) drugs

[FDCA 503(b)(1)]

Drugs that cannot be used safely without medical supervision.

- Examples?
  - Injectable* drugs
  - Drugs for conditions that are not amenable to self diagnosis
  - Drugs to treat serious conditions like heart disease, cancer, or fertility issues

*Injectable drugs are usually Rx, but insulin is not Rx in every state.

Registration: Domestic & Foreign

FDCA 510(b), (i) – Registration Requirement

- Manufacturers of drug in a bulk package & finished drug product
- Repackers and relabelers
- Control laboratories
- Domestic manufactures that pack/repack, label/re-label

NO or INADEQUATE ESTABLISHMENT REGISTRATION?

- Drug may be misbranded under FDCA 502(o) and subject to import refusal per FDCA 801(a)(3)

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 section 502(o) and subject to import 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 drug product: 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]*

CDER New Drug Approval (NDA/ANDA/BLA)

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

Approved drug must be:

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

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*)
- Adequate directions for use (*21 CFR 201.5*)

Drug Label Requirements

502(f)(1) – Misbranding and exemptions

- 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

Imports Affirmations of Compliance

- An Affirmation of Compliance (AofC) code, transmitted at the FDA line level, is one data element used in the entry review screening process.

- Examples: NDA, AND, NDC, REG, CFR, UFC

- While submission of this information is voluntary, transmission of the data may expedite initial screening and further review of an entry.

http://www.fda.gov/ForIndustry/ImportProgram/ucm349871.htm

Using an AofC

Questions:

A valid NDC number means 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

Questions:

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

Imported Drug

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 in sale in the country in which it was produced/exported

(3) is adulterated, misbranded, or in violation of section 505 of the act or food contains an approved drug …

801(a)(3)

- Adulteration (FDCA 501)
  - Includes GMP issues
- Misbranding (FDCA 502)
  - Lack of adequate directions for use or evidence of qualification for exemption
- Violation of FDCA 505
  - new drug without an application
  - includes violation of IND requirements

Adulteration & Imports

- cGMP and inspection status* (FDCA 501(a))
  - Investigational new drugs
  - Pre-approval products
- Labeling
  - 501(b) monograph or compendial
  - 501(c) non-monograph or compendial
- Analysis (certificates or testing)
  - 501(d) reduction in quality or substitution

**Inspection Classification Database Search*
http://www.accessdata.fda.gov/scripts/inspsearch/

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.
  - Drug in a bulk package
  - API – Active Pharmaceutical Ingredient
  - Drug Products – finished dosage form, Rx or OTC

Labeling and Shipping drugs in bulk packages (e.g. API)

Before your firm can label and ship a drug in a bulk package 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, BLA 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, ANDA, BLA or supplement approval

Exemptions from Misbranding
[21 CFR 201.122(a)]

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

Exemptions from Misbranding
[21 CFR 201.122(a)]

Labeling must have at least the statement:

"Caution: for manufacturing, processing, or repacking"

and

"Rx only" – if in all dosage forms in which the bulk drug may be used is subject to a human prescription *[503(b)(1)]*

Exemptions from Misbranding *[21 CFR 201.122(a)]*

Useful Information to make available at importation*:

- Drug (API) name and NDC number
- Name and address of the drug (API) manufacturer
- Approved NDA/ANDA/BLA number
- Supplemental NDA/ANDA/BLA number
- Intended or approved finished dosage drug product name and NDC number

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

Misbranding Exemption Summary *[21 CFR 201.122(a)]*

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

Supplements & Pending Application

- NDA/ANDA/BLA sponsors can work with the CDER review team to ensure application or supplement to an application include explanations of pending status
- If pending supplemental application requires FDA review, the pending status may be an appearance of a violation and support detention for safety or efficacy concerns when no explanation is available
- Violative Foreign Inspection Results
  - Entry may be detained

OAI: Official Action Indicated (gross CGMP violations)

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

Firm Information Not Found

(Drug application information not found by FDA entry review)

Useful Information to keep handy:

1. APIs included in original or initial application:
- Copy of the documents from original submission showing the drug supplier (e.g. CMC information submitted)
- 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)

Drugs for Pre-Submission Batches *[21 CFR 201.122]*

New Drug Application Pre-Submission Batches

- Drug used to conduct the studies needed to generate data required to submit a new drug application or supplemental new drug application
- FDA may exercise enforcement discretion

Useful Information to submit upon importation:

- Explanation of drug intended use
  - Example: bioequivalence or bioavailability with adequate reference to the applicable regulation

Drug for Pre-Submission Batches *[21 CFR 201.122]*

Useful Information to submit upon importation – Cont.:

- Drug name and NDC #
- Drug manufacturer name and address
- U.S. Consignee name and address
- Must be labeled as per *21 CFR 201.122*
- For supplemental new drug application – you may include NDA/ANDA number to be supplemented and NDC # of finished product

Drug in Bulk Package for OTC

Including Pending and Final Monographs

Labeling (Must State):

- "Caution: for manufacturing, processing, or repacking" (see drug label requirement slides)

Useful Information to provide upon importation:

- Name and NDC # of product to be manufactured with the drug in a bulk package
- A statement or reference justifying why approval is not required for the finished drug product
- Drug label content demonstrating compliance with *21 CFR 201.122*

Imported Drug in a Bulk Package
Summary

Drug may be exempt from misbranding when:

- meets certain labeling requirements
- is not used to manufacture a finished drug that is an unapproved new drug*
- is 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*

Drug in a Bulk Package Summary cont…

Drug may be imported to manufacture…

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

Rx Imports under 801(d)(1)
Prescription Drug Marketing Act (PDMA)

- Exported Rx drug products (i.e. subject to FDCA 503(b)) may be re-imported only by the original manufacturer
- 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)]

- Permit importation of violative articles of drug, i.e. misbranded, adulterated, unapproved, if the importer provides certain information to FDA at the time of the initial importation into the United States.
- Importer affirms in writing imported drugs will be further processed into products exported by initial owner/consignee in accordance with section 801(e) or 802 of the Act.
- FDA must be provided with certain information:
  - Written statement that article (finished dosage form or API) is to be further processed, and identification of all resultant manufacturers, processors, packers, distributors or any entity that had possession of the article
  - Certificate(s) of Analysis to identify the article
  - Records when requested

Secure Supply Chain Pilot Program

- Voluntary program which started in February 2014 (see Federal Register 78 FR 51192)
- Selection process is closed
- Program scheduled to conclude February 2016
- CDER approved drugs
- Up to five (5) foreign sourced drugs per applicant
- The program enables qualified firms to receive expedited imports entry review for the importation of the selected drugs in bulk packages and finished drug products
- Participants must have a validated secure supply chain protocol per Customs and Border Protection C-TPAT program Tier II or Tier III

PLAIR

(Pre-Launch Activities Importation Request)

Background:

- Section 505(a) of the FD&C Act prohibits the introduction of a new drug into interstate commerce unless there is an approved application filed for that drug.
- Firm(s) not following the PLAIR procedures will be subject to normal entry procedures.

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

PLAIR

Draft Guidance* for Industry issued July 2013

- CDER regulated NDA, ANDA or BLA
- 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 market launch based upon anticipated approval
- Does not apply to bulk ingredients or pending supplements
- Drug product may require minimal further processing such as final packaging and/or labeling
- Drug product may be in final packaged form

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

PLAIR cont …

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.

PLAIR cont…

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

Overall PLAIR review process is about two weeks.

PLAIR cont…

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.

PLAIR cont…

Who are the main contacts?

CDER:

CDER-OC-PLAIR@fda.hhs.gov

ORA/Division of Import Operations:

DIOPPLAIR@fda.hhs.gov

DRUG Import Alerts

55-05: DWPE of finished dosage drug products, active pharmaceutical ingredients, and inactive ingredients for potentially hazardous microbiological contamination

66-40: Drugs manufactured in violation of GMPs

66-41: Unapproved New Drugs

66-66: Misbranded APIs

66-72: Unapproved/misbranded drugs

99-32: Detention Without Physical Examination Of Products From Firms Refusing FDA Foreign Establishment Inspection

99-34: Drug and Device Firms without a valid drug or medical device firm registration

End

- Thank you!
- Email Imports Questions to:

  cderimportsexports@fda.hhs.gov