The Importation of Human Drugs: Labeling and Other FDA Compliance Issues

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Summary of the Importation of Drug Products
CBP and FDA

• U.S. Customs and Border Patrol ("CBP") is the initial authority for all imported products

• FDA is responsible for assuring the safety and effectiveness of domestic and imported drugs
FDA’s Role

• Screening of FDA specific data:
  – Country of origin, product code, manufacturer, shipper, affirmations of compliance, quantity and value of articles, approval status, establishment listing and registration, history of products and/or manufacturer (import alerts or bulletins).

• If product is not flagged for further review:
  – FDA never physically examines the product
  – Product gets a “may proceed”
  – Once the rest of the CBP entry process is done, product is no longer in “import status”
FDA’s Role

• If product is flagged for further review, FDA staff may:
  – Review the entry information or documentation
  – Request additional information or documentation
  – Conduct an exam or take a sample for analysis
FDA’s Role

• Sampling
  – 21 U.S.C. § 381(a) and 21 C.F.R. § 1.90
  – FDA staff usually collects the sample (MOU with CBP)
  – FDA must issue a notice of sampling
  – Importer must hold the goods until results come back
  – Failure to hold is violation of bond, not of the FDCA
FDA Refusal

- After review, FDA may issue a “may proceed” or may start the refusal process
- Refusal process:
  - FDA issues a Notice of FDA Action (notice of detention and hearing) giving the basis for refusal (21 C.F.R. § 1.94)
  - “Hearing” is very informal; work with the District Office
    - May consult CDER
  - Owner or consignee can either:
    - Challenge law or evidence; or
    - Apply for reconditioning in some instances (21 U.S.C. § 381(b); 21 C.F.R. § 1.95). The reconditioning must be approved by FDA. For example, can petition to re-label.
FDA Refusal

• Depending on circumstances, FDA can admit the product ("may proceed"), allow reconditioning, or refuse admission

• If refused, the product must be exported within 90 days or it is destroyed
  – The bond is used to ensure that the product is exported or destroyed
    • Under the bond, CBP can demand "redelivery". Failure to redeliver (e.g., for sampling, export/destruction) can result in liquidated damages up to 3x the value of the goods.
FDA’s Authority Over Imports

• Under 21 U.S.C. § 381(a), FDA may (shall) refuse admission if the drug product appears to be:
  – Produced under insanitary conditions;
  – Forbidden or restricted in sale in the country it was produced in or exported from; or
  – Adulterated, misbranded, or an unapproved new drug
• Recent court decisions rejecting FDA’s use of enforcement discretion
  • Cook v. FDA
  • K-V Pharmaceutical Co. v. FDA
FDA’s Authority Over Imports

• The appearance of a violation may be based on “the examination of such samples or otherwise”
  – Refusal could be based on FDA experience or other credible information from other sources

• Generally, FDA needs some affirmative evidence, not just that FDA lacks evidence that product is in compliance
  – Section 707 of FDASIA added 21 U.S.C. § 351(j) to the FDCA to deem adulterated a drug when an inspection is delayed, denied, limited or refused
FDA’s Authority Over Imports

- FDA can also refuse admission for:
  - OTC human drug or dietary supplement for adverse event violations (21 U.S.C. § 381(a), fourth sentence).
  - Drugs for registration violations (21 U.S.C. § 381(o))
    - the law now deems any drug misbranded if it is imported from an unregistered foreign facility (21 U.S.C. § 352(o))
  - FDA and CDC have authority to prevent the transmission of communicable diseases, including at importation (section 361 of the PHSA)
    - CDC generally has the lead
    - Governs tissue and HCT/P importation
FDA’s Authority Over Imports

• FDA can seize products. 21 U.S.C. § 334
  – Imports are in interstate commerce and can be seized upon arrival
  – Imports can be seized after admission
  – Burden is civil judicial standard, not “appearance” of a violation
  – Generally, if the government wants to seize, it won’t refuse entry under 21 U.S.C. § 381(a) due to its provision for exportation
Potential Drug Importation Compliance Issues
Unapproved New Drugs

• “New drugs” must be approved by FDA before marketing. 21 U.S.C. § 355(a)

• Requires approval of an application filed pursuant to 21 U.S.C. § 355(b) or § 355(j) is in effect for such drug. 21 U.S.C. §§ 331(d), 355(a)

• “New drug” unless it is GRASE and has been used to a material extent or for a material time with that labeling
Unapproved New Drugs

• Unapproved drugs will be denied entry into the U.S.
  – FDA may exercise enforcement discretion, particularly to avert drug shortage
  – Recent court decisions put this at risk, however

• Rx drugs must have FDA approval
  – A Rx drug that lacks an approved application lacks adequate directions for use as a matter of law and therefore is misbranded
  – “Back-Door” Unapproved New Drug Charge

• Cosmetic vs. Drug
Over-the-Counter ("OTC") Drugs

• Certain drugs may be dispensed only by prescription ("Rx only"); all other drugs are OTC

• OTC = Drugs that FDA believes can be labeled for safe, immediate use without a physician’s supervision

• OTC drugs may be marketed (1) under a new drug application or (2) under a regulation known as a "monograph" which does not require FDA pre-market approval
OTC “Monograph” Drugs

• OTC drug monographs establish conditions under which classes of OTC drugs may be marketed without FDA pre-approval

• Monograph products must contain the ingredients specified in the monograph and bear labeling that incorporates the indications, warnings, and directions for use specified in the monograph. 21 C.F.R. § 330.1

• Must make sure product strictly conforms to a monograph; if not it is deemed an unapproved new drug and misbranded. 21 C.F.R. § 330.1
A Drug is Misbranded if –

• Its labeling is false or misleading. 21 U.S.C. § 352(a)
  – This sweeps broadly and prohibits labeling that has the capacity or tendency to deceive. For example:
    • Exaggerates a drug’s effectiveness
    • Suggesting that a drug is safe, when it may be dangerous

• Its labeling fails to contain “(1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count . . . .” 21 U.S.C. § 352(b)
  – For example, violation if label failed to state quantity of contents or the name of the manufacturer
A Drug is Misbranded if –

• Its labeling fails to display required information prominently and in understandable terms. 21 U.S.C. § 352(c)
  – The required information must appear on a portion of the label that is usually displayed under conditions of purchase. 21 C.F.R. § 201.15(a)(1)
  – The regulations address the factors that contribute to lack of conspicuousness. 21 C.F.R. § 201.15(a)(6)
    • Such as size or style of type, insufficient background contrast, designs that obscure, or crowding with other written, printed, or graphic matter
  – Must be in English (except for non-English U.S. territory)
A Drug is Misbranded if –

• Its labeling does not contain the name of the drug and ingredients. 21 U.S.C. § 352(e)
  – Must bear the established name of the drug and may not bear any other non-proprietary name, except the applicable chemical name or formula
  – The label must also list in alphabetical order the names of all inactive ingredients
  – All the information must appear on the drug’s carton, outer container or wrapper, or on a leaflet with the package. 21 C.F.R. § 201.10(i)(2)
A Drug is Misbranded if –

• Its labeling fails to bear adequate directions for use. 21 U.S.C. § 352(f)(1)
  – No directions or no directions for a promoted use
  – Directions lack scientific substantiation
  – Unapproved new Rx drug lack adequate directions for use as a matter of law
  – Rx drugs approved by FDA are exempt from adequate directions for use, provided that they are dispensed in accordance with 21 U.S.C. § 353, and that other conditions are met. 21 U.S.C. § 353(b)(2); 21 C.F.R. §§ 201.100, 201.115
  – OTC drugs comply by conforming to OTC monograph

• An OTC drug is misbranded if it bears the “Rx” symbol. 21 U.S.C. § 353(b)(4)(B)
A Drug is Misbranded if –

- Its labeling fails to bear adequate warnings. 21 U.S.C. § 352(f)(2)
- A drug must be packaged and labeled in conformity with official compendium’s standards. 21 U.S.C. § 352(g)
- Drug is misbranded if establishment not registered or if drug not listed. 21 U.S.C. § 352(o)
- Lacks Expiration dates. 21 C.F.R. §§ 201.17, 211.137
- Lacks Lot number. 21 C.F.R. § 201.18
OTC Labeling Requirements To Remember

• General Requirement – artwork may not hide or obscure any required labeling
• Statement of Identity (“SOI”)
• Net Quantity of Contents Declaration
• Name and Place of Business of Manufacturer, Packer, or Distributor
• Drug Facts Panel (“DFP”)
• Adverse Event Reporting Information
• Miscellaneous (tamper evident statement; expiration dating; country of origin; NDC number [not legally required])
Registration and Listing
21 U.S.C. 360(i); 21 C.F.R. § 207.40

• 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 of foreign establishment
  – Designate a U.S. agent
  – Provide names of each known importer and person who imports or offers for import
  – List all drug products imported or offered for import into the U.S. (Listed products are assigned NDC #)

• If NDC appears on the label it must comply with regulation 21 C.F.R. § 207.35(b)(3)
Active Pharmaceutical Ingredient Requirements

• Intended for use in a product approved in NDA, ANDA, or supplement. 21 C.F.R. § 201.122(a)

• Intended for use in product subject to an IND. 21 C.F.R. § 201.122(b)

• Intended for use in product subject to a pending/near NDA or ANDA or supplement approval. 21 C.F.R. § 201.122(b)

• Intended for use in teaching, law enforcement, research, and analysis and not for use in humans. 21 C.F.R. § 201.125
Active Pharmaceutical Ingredient Requirements

• API labeling must bear “Caution: for manufacturing, processing, or repacking”
• “Rx only” when most dosage forms to be manufactured are Rx
• Must comply with general labeling provisions under 21 C.F.R. § 201.1
• API for IND labeling must also bear “in the preparation of a new drug or new animal drug limited by federal law to investigational use”
Investigational New Drug Requirements

• Must comply with the IND import requirements. 21 C.F.R. § 312.110(a)
  – Subject to an IND under 21 C.F.R. § 312.40

• Labeling must comply with 21 C.F.R. § 312.6
  – “Caution: New Drug—Limited by Federal (or United States) law to investigational use.”

• Finished drug intended for IND use in laboratory research animals or in-vitro testing. 21 C.F.R. § 312.160
  – “Caution: Contains a new drug for investigational use only in laboratory research animals, or for tests in-vitro. Not for use in humans”
CGMP and Adulteration

• A drug is adulterated if it is not manufactured in compliance with current good manufacturing practice (CGMP). 21 U.S.C. § 351(a)(2)(B); 21 C.F.R. Parts 210 and 211
  – Statutory obligation applies to API
• Foreign inspections of pharmaceutical manufacturers can lead to an import refusal and an import alert
• FDA may implement an import alert and detain drug product without physical examination when an FDA inspection has revealed that a firm is not operating in conformity with GMP
• DWPE of firms remains in effect until FDA is satisfied that the appearance of a violation has been removed, either by reinspection or submission of appropriate documentation
Country of Origin

• Country of Origin is determined using a standard set forth in the Customs law (see 19 U.S.C. § 1304 and 19 C.F.R. Part 134) and the Trade Agreements Act (“TAA”) (19 U.S.C. § 2518)

• Generally the COO is the API source country, unless the product is substantially transformed
Questions?

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