



U.S. Food and Drug Administration

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Human Drug Exports Compliance





Export of Human Drugs and Human Drug Components

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Import Operations Branch (IOB)

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Outline

- Import Operations Branch (IOB)
- Definitions
- Laws and Regulations
- Export Certificates

Import Operations Branch (IOB)

- Created on June 6, 2011 when the CDER Office of Compliance was reorganized. The IOB:
- Serves as an FDA focal point for compliance issues related to imported and exported human drugs.
- Consults with and provides guidance to FDA field offices and consults with the field on import and export issues for specific drug products.
- Coordinates with the Office of Regulatory Affairs (ORA) on policies, programs and procedures related to field operation needs.
- Reviews requests, and issues, when appropriate, export certificates.
- Develops and provides guidance on human drug import and export policies and procedures.



Definitions

What is a drug?

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 USP/NF, HPUS or any supplement to them
- Intended for use as a component of a drug

Is it a Drug?

- Regulation 21 CFR 201.128, defines the term “intended uses”
 - Intent is determined by labeling, advertising matter, oral or written statements
- Finished products, active pharmaceutical ingredients (APIs), excipients, and labels/labeling for such products are defined to be drugs. Chemicals can be drugs, but not all chemicals are drugs
- GHB, GBL, DMSO, are chemicals but can also be drugs

Is it a new drug?

Definition: "New" drug *[FFDCA 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 or abbreviated new drug application (NDA/ANDA) to be legally marketed in the U.S. or by an investigational new drug application (IND) *[FFDCA Section 505]*
- Rx and Over-the-Counter (OTC) drugs can both be new drugs

Is it an OTC or Rx drug?

Rx Drug - *[FFDCA 503(b)(1)]*

Drugs that cannot be used safely without medical supervision.

– Examples?

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

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

Is it an Over-The-Counter (OTC) drug?

- A drug for which adequate directions for use can be written (Section 502(f)(1) of the FFDCFA and Regulation 21 CFR 201.5
- 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

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))

Drug or Dietary Supplement?

- A dietary supplement (DS) must meet definition of DS 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, or mitigate disease
- Products that otherwise can be dietary supplements are drugs if they contain an ingredient such as sildenafil, the active ingredient in Viagra

Drug or Cosmetic?

- A cosmetic (Section 201(i)) is for cleansing, beautifying, promoting attractiveness, or altering the appearance.
- However, a “cosmetic” with anti-aging claims is a drug.
- Antimicrobial soap and antiperspirant/deodorant products are both drugs and cosmetics.
 - These products must meet both the drug and cosmetic regulations.



Human Drug Exports – What Laws and Regulations Apply?

Human Drug Exports

- FDA is responsible for assuring the safety and effectiveness of drugs and other products manufactured in the U.S. for domestic consumption and export. Other agencies such as CBP, DEA, and USDA also have responsibility.
- Export provisions for drugs in the Food, Drug, and Cosmetic Act (FDCA) are fairly complicated. Understand which product you wish to export and the requirements for its legal exportation.
- Good starting point is the Guidance for Industry: Exports Under the FDA Export Reform and Enhancement Act of 1996.

FDA Export Reform and Enhancement Act of 1996

- The 1996 Act addressed the industry's main problems and concerns regarding the exportation of human drugs.
- Designed to ease restrictions on exportation and importation of unapproved products.
- **Does not affect the export of approved products.**
- Amended sections 801 and 802 of the FDCA as well as section 351(h) of the Public Health Service Act.
- Eliminates the requirement for prior FDA approval exporting unapproved new human drugs in most cases.

FDA Export Reform and Enhancement Act of 1996 (continued)

- Significantly expanded the list of countries to which **unapproved** drugs can be exported without prior FDA approval.
- Authorized the export of **unapproved** drugs intended for use in clinical investigations.
- Authorized the export of certain **unapproved** drugs to a listed country in anticipation of marketing approval.
- Created a simple notification process.
- Authorized FDA to permit export of **unapproved** drugs intended to treat tropical or other diseases that are “not of significant prevalence in the United States.”

Export of an Approved Product for Commercial Use

- A drug lawfully marketed in the U.S. can be exported anywhere without prior FDA approval or notification.
- Product must comply with the importing country's laws.
- Other federal regulatory agencies to consider including DEA, CBP, DOC.

Export Under Section 801(e)

- A product intended for export that may not be marketed in the U.S. because it is considered adulterated or misbranded may nevertheless be exported to **any country if it:**
 - (1) Accords to the specifications of the foreign purchaser;
 - (2) Is not in conflict with the laws of the country to which it is intended for export;
 - (3) Is labeled on the outside of the shipping package that it is intended for export; and
 - (4) Is not be sold or offered for sale in domestic commerce

Export Under Section 801(e) (continued)

- As a statutory exemption, this provision is to be construed narrowly. **The exporter bears the burden of demonstrating that the criteria of the exemptions are met.**
- During routine inspections, FDA will evaluate whether a firm has complied with section 801(e)(1). Records demonstrating compliance must be kept.
- FDA's record keeping requirements that implement section 801(e)(1) are found in 21 CFR 1.101(b).

Definitions: Accords to the Specifications of the Foreign Purchaser

- We recommend that the exporting firm keeps records which contain sufficient information that the product matches the specs requested by the foreign purchaser.

Should include:

- Details about the product (e.g. dosage strength, dosage form).
- Details about the product's compliance with a particular manufacturing standard.
- English-language translation of the specifications document.

Is Not in Conflict With the Laws of the Importing Country

Under 21 CFR 1.101(b)(2), two possible ways to show this.

- 1) May obtain a letter from the foreign country authority documenting that the product has marketing approval or will not be in conflict with the importing country's laws, or
- 2) A notarized certification by a responsible company official in the U.S. that the product does not conflict with the laws of the importing country.

For Export Only

- The company labels the outside of the shipping container that the product is intended for export.
 - “For export only” is adequate. 21 CFR 1.101(b)(3)

Product Is Not Sold or Offered for Sale in Domestic Commerce

- Company should maintain records concerning the product, and its labeling. Records of similar products offered for sale in the U.S. should also be maintained.
 - A statement on the labeling such as “Not for sale in the United States” may be sufficient.

Re-importation of Exported Rx Drugs (Section 801(d)(1))

- Except as provided below, no drug subject to section 503(b) or composed wholly or partly of insulin:
 - Which is manufactured in a State and exported.
 - May be imported in the United States unless:
 - The drug is imported by the manufacturer of the drug.
 - The Secretary may authorize the importation of a drug the importation of which is prohibited by paragraph one above.

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

- Under old law, importation solely for export was illegal.
- Section 801(d)(3) allows the importation of any component of a drug that will be further processed or incorporated by the initial importer or consignee into a drug that will be exported under sections 801(e) or 802.
 - The terms “processing and incorporation” are not further defined in the Export Reform Act.

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

- The 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 that the article (finished dosage form or API) is to be further processed, and the resultant manufacturer, 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)] - continued

- 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)]:
 - False information and statement
 - Introduction into interstate commerce any article (including finished)
 - Not submitting and maintaining records and COA

Import for Export (continued)

- Conditions for Importation:
 - Importer must notify the FDA at the time of the initial importation that the imported article will be further processed into a drug by the initial importer or consignee into a product that will be exported.
 - FDA can refuse admission of the product if notice is not provided.
 - Any imported article not incorporated or further processed must be destroyed or exported. If the product cannot be exported, it must be destroyed.
 - There is no deadline on when the product must be incorporated/further processed or destroyed.
 - Failure to export or destroy the product will subject the product to seizure action as an adulterated or misbranded drug.

Specific Labeling Requirements (Section 801(f)(1) & (2))

- If a product is exported to a country that has different or additional labeling requirements or conditions for use than the U.S., and if the country requires the labeling to reflect those conditions, the product may be:
 - Labeled in accordance with such requirements if it is also labeled in accord with the requirements of the FDCA.
 - If the labeling of the product includes “conditions for use” that have not been approved under the FDCA, the labeling must state that such conditions have not been approved under the FDCA.
 - The provision applies to products exported under section 801(e)(1), not section 802.

Specific Labeling Requirements (continued)

- In order to comply with the specific labeling requirements of section 801(f)(2), the manufacturer should place a statement on the labeling concerning the uses not approved in the U.S. when an unapproved use appears.
- The statement identifying the unapproved uses in the U.S. should be in the foreign country's language, although section 801(f)(2) does not explicitly require this.

Export of Unapproved Drugs Under Section 802(b)(1)

- A drug which requires approval under section 505 may be exported to any country, if the drug complies with the laws of that country and has valid marketing authorization in one of the listed (tier-one) countries.
- Listed countries include Australia, Canada, Israel, Japan, New Zealand, Switzerland, or South Africa; or in the European Union, or a country in the European Economic Area.
- The Export Act permits the Secretary of HHS to add countries to the list under specific conditions outlined in section 801(b)(1)(B). FDA does not have the authority to add countries.

Export Notification (802)(b)(1)

- **The Export Act requires the exporters to identify the country only if it is not a listed country.** We advise the exporter to identify the importing country in all cases.
- Must provide simple notice to FDA for export of unapproved new drugs under section 802(b)(1). Must:
 - Provide notice when exporter first begins to export
 - Maintain records of products and countries where exported
 - We recommend that the simple notification for export under 802(b)(1) contain the following information.
 - Product name
 - Generic name
 - Description of its strength and dosage form

Export Notification (802)(b)(1) (continued)

- Exported drug must comply with section 802(f), which in relevant part, prohibits export if any of the following criteria are met:
 - Drug is not manufactured, processed, packaged, or held in substantial conformity with cGMPs.
 - The drug is adulterated.
 - Drug does not meet the four requirements described in section 801(e)(1).
 - The drug is the subject of a determination by FDA that the probability of re-importation of the drug would present an imminent hazard to the public health and safety of the United States.

Export Notification (802)(b)(1) (continued)

- Exported drug must comply with section 802(f), which in relevant part, prohibits export if any of the following criteria are met:
 - The drug labeling is not in accordance with the requirements and conditions for use in the export target country.
 - The drug is not labeled in the language and units of measurement of the export target country.
 - Drug is not promoted in accordance with the foreign labeling requirements of the above.
 - In making a finding under the above three provisions, the Secretary (FDA) is required to consult with the appropriate public health official in the affected country.

Export of Unapproved New Drugs to an Unlisted Country (802)(b)(2)

- An unapproved drug may be directly exported to an unlisted country if the drug complies with the laws of that country and has valid marketing authorization by the responsible authority in that country.
- FDA must determine that the foreign country has statutory or regulatory requirements which:
 - Requires the review of drugs for safety and efficacy by a government entity, and which authorizes approval of drugs, which trained and experienced experts have determined to be safe and effective.
 - The experts must be employed by or acting on behalf of the foreign government entity and base their decision on adequate and well controlled investigations.
 - Statutory or regulatory requirements concerning cGMPs
 - Labeling and promotion be in accordance with the approval of the drug.
 - Information to the FDA of the country's statutory and regulatory requirements.

Export of Unapproved Drug Under Section 802(b)(3)

- Unapproved drugs may be exported to an unlisted country under section 802(b)(3) of the FDCA if the conditions for export under section 802(b)(1) and 802(b)(2) of the FDCA cannot be met.
- This section permits a firm to petition the FDA to authorize exportation to an unlisted country.
- Export under 802(b)(3) involves the submission of scientific evidence and pertain to a specific drug intended for export to a specific country.

Summary - Exporting Unapproved New Drugs [section 802]

1. An unapproved new drug can be exported to any country if the drug complies with the laws of that country and has valid marketing authorization in a “listed” country [802(b)(1)(A)] The list can expand.
2. If drug intended for export to an unlisted country but none of the listed countries has approved the drug for marketing, the drug may be exported [802(b)(2)]
3. If a drug cannot be exported under 1 or 2, it may be exported [802(b)(3)] but "credible scientific evidence" exists and is accepted by FDA. The agency has 60 days to act on the request to export.

Must provide written notification to FDA when exporting human drugs under 802 (21 CFR 1.101(d)) except INV drugs (802(c)) or market authorization (802(d))

Export of Unapproved New Drug for Investigational Use (section 802(c))

- A drug intended for investigational use in any listed country may be exported in accordance with the laws of that country and shall be exempt from section 505(i) of the FDCA.
 - If exporting an unapproved drug for investigational use to a listed country, you may proceed under:
 - An “approved” IND, section 802(b)(1), section 802(c), or 21 CFR 312.110.
 - If exporting an unapproved drug to an unlisted country, you may proceed under:
 - An approved IND, section 802(b)(1), or 21 CFR 312.110 if certain conditions are met.
 - Transshipment of investigational drugs from a listed to an unlisted country is not permitted.

Export Under Section 802(d) and Section 802(e)

- Section 802(d)
 - A drug intended for formulation, filling, packaging, labeling, or further processing in anticipation of market authorization in any listed country may be exported for use in accordance with the laws of that country.

- Section 802(e)
 - A drug which is used in the diagnosis, prevention, or treatment of a tropical disease or another disease not of significant prevalence in the United States and which otherwise does not otherwise qualify for export under this section shall, upon approval of an application, be permitted to be exported if certain conditions are met.

Notification and Recordkeeping (21 CFR 1.101)

- The exporter must maintain records of the products exported and the countries to which they were exported. These records should contain the following information:
 - Product trade name and generic name.
 - A description of its strength, dosage form, and lot/control number.
 - The consignee name and address.
 - Date and quantity of product exported.
 - Records must be kept and maintained at the site from where the products were exported for at least three years from date exported. FDA may review these records during an inspection.
 - Records are kept separate from any other records.

Transport and Exportation (T&E)

- Products are transported through the U.S. to be exported.
- CBP regulation 19 CFR 18.10, "Kinds of Entry", lists the various entries and withdrawals that may be made for merchandise transported in bond. One kind of entry is the transportation and exportation (T&E) entry.
 - A T&E filed with CBP, allows a party to transport merchandise in bond through the U.S. and export the merchandise intact to a foreign destination without the payment of duties. (See 19 U.S.C. 1553, 19 CFR 18.11, and 19 CFR 18.20.)

Transport and Exportation (T&E) (continued)

- Possible weaknesses in T&E. Product is not re-exported.
- 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 the second shipment contained Rx steroids
- Products were seized

Drug Export Certificates

What are FDA Export Certificates?

- Firms exporting products from the United States are often asked by foreign customers or governments to supply a “certificate” for products regulated by the FDA. A certificate is a document prepared by the FDA that contains information about a product’s regulatory or marketing status.
- Section 801(e)(4) of the Act provides that FDA shall, upon request, issue certificates for human drugs and biologics, animal drugs, and devices that either meet the applicable requirements of the Act and may be legally marketed in the US, or may be legally exported under the FDCA although they may not be legally marketed in the US .
- Export certificates are issued for both finished drug products and APIs. Export certificates may bear a remarks section statement concerning the status of the product.

Export Certificates (continued)

What Types of Export Certificates are issued by FDA for Human Drugs?

FDA issues the following types of Export Certificates:

- The "**Certificate to Foreign Government**" is for the export of products that can be legally marketed in the United States.
- The "**Certificate of Exportability**" is for the export of drug products that cannot be legally marketed in the US, but meet the requirements of Sections 801(e) or 802 of the Act and may be legally exported.
- The "**Certificate of a Pharmaceutical Product**" conforms to the format established by the World Health Organization (WHO) and is intended for use by the importing country when considering whether to license the product for sale in that country.

Export Certificates for Unapproved Drugs

- The 1996 FDA Export Reform amendments provide for the FDA to issue certificates for exports of certain drugs even though they are not allowed to be marketed in the United States.
- For human drugs, FDA issues a Certificate of Pharmaceutical Product, containing a notation that the product is unapproved.

Export Certificates (continued)

- FDA performs routine inspections of US manufacturers that are registered and listed with FDA for compliance with current GMP regulations.
- FDA bases its attestation of compliance with current GMP regulation on the manufacturer's most recent FDA inspection.
- During a routine inspection for compliance with GMP, the US manufacturer is evaluated by FDA to determine if they can manufacture, process, package, and hold a product to assure that it meets the requirements of the Act as to safety, identity, strength, quality, and purity.

Export Certificates (continued)

What is meant by FDA, when we attest to compliance with current Good Manufacturing Practice (GMP) regulations in an Export Certificate?

- GMP for drugs are the requirements for the methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug (including a biologic) to assure that such drug meets the requirements of the Act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess (21 CFR Part 210, 211).
- Contact for Branch is Betty McRoy at betty.mcroy@fda.hhs.gov for information concerning certificates.
- Export certificate requests should be mailed to FDA, CDER Export Certificate Program, 10903 New Hampshire Avenue, Building 51, Room 4249, Silver Spring, MD 20993.

Export Certificates (continued)

FDA will not issue a Certificate to Foreign Government, or a Certificate of a Pharmaceutical Product under section 801(e)(4) of the Act for products when the products do not meet the applicable requirements of the Act.

Additionally, such certificates will not be issued if FDA has initiated an enforcement Action (e.g., seizure/injunction).

Examples of circumstances for which certificates will not be issued include:

- manufacturing facility(ies) not registered or listed with FDA; and
- manufacturing facility(ies) for which FDA has no inspectional information.
- FDA will not issue Certificates of Exportability for products subject to section 802 of the Act if the manufacturing facility(ies) do not comply with current Good Manufacturing Practice regulations, unless the particular exported product is not affected by the specific GMP deficiencies.
- Product is not exported.

Export Certificates

- For human drugs issued under section 801(e)(4) of the FDCA, the agency may charge a fee of:
 - \$175 for the first certificate
 - \$90 for the second certificate with attachments for the same product(s) issued in response to the same request
 - \$40 for any subsequent certificates with attachments for the same product(s) issued in response to the same request

- The agency must issue the certificate within 20 days of receipt of a complete request for such a certificate to collect the fee.
 - The FDA has interpreted this to mean 20 working days.

References

- Federal Food, Drug and Cosmetic Act:
<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/default.htm>
- 21 Code of Federal Regulations (CFR):
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>
- OTC Drug Monographs:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/default.htm>
- Regulatory Procedures Manual (RPM) :
<http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm>
- Guidance for Industry: Exports Under the FDA Export Reform and Enhancement Act of 1996:
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm125799.htm>
- Guidance – FDA Export Certificates:
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125822.pdf>

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Thank you!

Questions?