

Guidance for Industry: Exports Under the FDA Export Reform and Enhancement Act of 1996

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Guidance for Industry: Exports Under the FDA Export Reform and Enhancement Act of 1996¹

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic and replaces FDA's previous guidance on exports entitled, "A Review of FDA's Implementation of the Drug Export Amendments of 1986." It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

This guidance document summarizes and explains the basic requirements and procedures under the FDA Export Reform and Enhancement Act of 1996 (Public Law 104-134, as amended by Public Law 104-180) for exporting human drugs, animal drugs, biological products, devices, food, food additives, color additives, and dietary supplements that may not be sold or distributed in the United States. This law amended sections 801 and 802 of the Federal Food, Drug, and Cosmetic Act (the Act), as well as section 351(h) of the Public Health Service Act, simplifying the requirements for exporting unapproved human drugs, biological products, and devices. In addition, the FDA Export Reform and Enhancement Act substantially reduced the requirements for exporting unapproved new animal drugs and provided a new option for exporting unapproved devices.

The 1996 Amendments did not change the general export requirements in section 801(e)(1) of the Act with respect to foods or cosmetics. This document provides guidance on these general export requirements under section 801(e)(1) of the Act for all products that are

¹ This guidance has been prepared by the Office of International Programs in the Office of the Commissioner in cooperation with the Center for Veterinary Medicine, Center for Biologics, Center for Devices and Radiological Health, Center for Drug Evaluation and Research, and Center for Food Safety and Applied Nutrition at the Food and Drug Administration.

This guidance document may be supplemented by other guidance documents on specific topics.

subject to this provision. Guidance is also provided on the export requirements for unapproved human drugs, biological products and devices in sections 801 and 802 of the Act resulting from the 1996 Amendments.

If a product meets the Act's requirements for sale and distribution in the United States, the Act has no additional restrictions on its exportation (i.e., sections 801 and 802 of the Act do not apply to such exports). However, other federal statutes or regulations administered by other federal agencies (such as the Department of Commerce) may apply.

This guidance document does not address export certificates and any associated fees. Information on these subjects can be found in FDA's Compliance Policy Guide 7150.01, "Certification for Exports", and FDA's Guidance for Industry, "FDA Export Certificates".

This guidance document also does *not* address the importation and subsequent exportation of certain articles under section 801(d)(3) and (d)(4) of the Act, which is sometimes referred to as the "import-for-export" provision. Although the draft guidance document on the 1996 Export Reform and Enhancement Act discussed the importation of certain components, parts, and accessories of human drugs, biological products, devices, food additives, color additives, and dietary supplements for further processing or incorporation into products intended for export, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002² significantly revised section 801(d)(3) of the Act. The revised statutory provision went into effect on September 9, 2002, and FDA announced, in a September 18, 2002, *Federal Register* notice (67 FR 58810), that it had revised the relevant FDA Regulatory Procedures Manual chapter to incorporate those changes.

Please note that a firm or product may be subject to additional statutory or regulatory requirements beyond those described in this guidance. For example, a firm may be subject to the establishment registration requirements under section 510 of the Act (21 U.S.C. 360). Please contact the appropriate FDA center for additional information. Additionally, exports involving controlled substances may be subject to requirements administered by the Drug Enforcement Administration. Exports of certain products or exports to specific countries

² Public Law 107-188, enacted on June 12, 2002.

may be subject to licensing and other requirements administered by the Department of Commerce or the Bureau of the Census.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Terms Used in This Guidance

This guidance uses the following terms:

“**Act**” means the Federal Food, Drug, and Cosmetic Act. Citations to specific sections of the Act will use the numerical sequence specified in the Act rather than the section numbers used in the United States Code (U.S.C.).

“**cGMP**” means current good manufacturing practice. For drugs and most biological products, cGMP regulations can be found at parts 210 and 211 (21 CFR Parts 210 and 211). For devices and biological products regulated as devices, cGMP regulations (referred to as quality systems regulations or QSR) can be found at part 820 (21 CFR Part 820). For blood and blood components, additional regulations can be found at part 606 (21 CFR Part 606).

“**FDA**” or “**agency**” means the Food and Drug Administration.

“**IDE**” means an investigational device exemption application. These are applications containing requests to use an unapproved device in clinical tests using human subjects. The regulations are authorized under section 520(g) of the Act (21 U.S.C. 360(g)), and the implementing regulations can be found at part 812 (21 CFR Part 812).

“**IND**” means an investigational new drug application. These applications are usually required for persons who intend to conduct clinical investigations involving products subject to section 505 of the Act (21 U.S.C. 355) or to the licensure provisions in section 351 of the Public Health Service Act (42 U.S.C. 262). The IND regulations are authorized by section 505(i) of the Act and are found at part 312 (21 CFR Part 312).

“**1986 Amendments**” means the Drug Export Amendments Act of 1986 (Public Law 99-

960). The FDA Export Reform and Enhancement Act of 1996 revised or eliminated most provisions in the 1986 Amendments.

“1996 Amendments” means the FDA Export Reform and Enhancement Act of 1996 (Public Law 104-134 and amended by Public Law 104-180).

“PHS Act” means the Public Health Service Act (42 U.S.C. 201 et seq.). Citations to specific sections of the PHS Act will use the numbers specified in the PHS Act rather than the section numbers used in the U.S. Code.

“PMA” means a premarket approval application. This is a marketing application for certain devices under section 515 of the Act. The PMA regulation is at 21 CFR part 814.

“312 Program” means the regulatory program used by FDA for permitting the exportation of investigational drugs or biological products for clinical use in foreign countries. The principal statutory authority for the 312 Program is section 505(i) of the Act, and the implementing regulation is at 21 CFR § 312.110.

III. Quick Guide

The chart below can be used to identify possible export routes for FDA-regulated products in various circumstances. You should examine the requirements of the cited export provision or provisions carefully to determine whether you can export a particular product in compliance with those requirements.

Type of Product	Status Under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act (PHSA)	Intended for Commercial Distribution or Investigational Use	Approved/ Legally Marketed in a Listed Country	Possible Export Provision Options and Relevant Guidance Document Chapter	Section 801(e)(1) applies?	Sections 802(f) and 802(g) apply?	Special Requirements
Drug (including Biological Products)	Approved as distributed in the U.S., but to be exported with different or additional labeling requirements or conditions for use	Commercial	n/a	801(f) See part VI	Yes	No	-
			Yes	802(b)(1) See part VII C and D	Yes	Yes	-
Drug (including Biological Products)	Requires approval under section 505 of the Act or licensing under section 351 of the PHSA, and does not have <u>OR</u> not in compliance with approval – includes drugs not in compliance with OTC monographs – or licensing	Commercial	Yes	802(b)(1) See part VII C and D	Yes	Yes	-
Drug (including Biological Products)	Requires approval under section 505 of the Act or licensing under section 351 of the PHSA, and does not have <u>OR</u> not in compliance with approval – includes drugs not in compliance with OTC monographs – or licensing	Investigational	Yes	802(b)(1) See part VII C and D	Yes	Yes	-
			n/a	802(c) See part VIII	Yes	Yes, except for notification under (g)	-

Type of Product	Status Under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act (PHSA)	Intended for Commercial Distribution or Investigational Use	Approved/ Legally Marketed in a Listed Country	Possible Export Provision Options and Relevant Guidance Document Chapter	Section 801(e)(1) applies?	Sections 802(f) and 802(g) apply?	Special Requirements
Drug (including Biological Products)	Requires approval under section 505 of the Act or licensing under section 351 of the PHSA, and does not have <u>OR</u> not in compliance with approval - includes drugs not in compliance with OTC monographs - or licensing	Investigational	n/a	21 CFR 312.110	-	-	See provisions of 312.110 for specific options and requirements
Drug (including Biological Products)	Requires approval under section 505 of the Act or licensing under section 351 of the PHSA, and does not have <u>OR</u> not in compliance with approval - includes drugs not in compliance with OTC monographs - or licensing	Commercial, but exported to a listed country for further formulation, processing, etc.	No, but exported in anticipation of market authorization	802(d) See part IX	Yes	Yes, except for notification under (g)	-
Drug (including Biological Products)	Requires approval under section 505 of the Act or licensing under section 351 of the PHSA, and does not have <u>OR</u> not in compliance with approval - includes drugs not in compliance with OTC monographs- or licensing	Commercial; exported to an unlisted country	No.	802(b)(2) or 802(b)(3) See part VII F	Yes	Yes, except for notification under (g)	Both require a submission to FDA and a determination by FDA before the export can begin
Drug (including Biological Products)	Requires approval under section 505 of the Act or licensing under section 351 of the PHSA, and does not have <u>OR</u> not in compliance with approval - includes drugs not in compliance with OTC monographs - or licensing	Intended for use in a tropical disease or other disease not of significant prevalence in the U.S.	No	802(e) is an option for an export to an unlisted country if the product does not qualify for export under any other provision of section 802 of the Act See part X	Yes	Yes, except for notification under (g)	Requires approval of an application to FDA before the export can begin

Type of Product	Status Under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act (PHSA)	Intended for Commercial Distribution or Investigational Use	Approved/ Legally Marketed in a Listed Country	Possible Export Provision Options and Relevant Guidance Document Chapter	Section 801(e)(1) applies?	Sections 802(f) and 802(g) apply?	Special Requirements
Drug (including Biological Product)	Adulterated or Misbranded <u>BUT</u> does not require approval under section 505 of the Act or licensing under section 351 of the PHSA	Commercial	n/a	801(e)(1) See part V A and B	Yes	No	–
Insulin or Antibiotic Drug	Adulterated or Misbranded (irrespective of status under section 505 of the Act or section 351 of the PHSA	Commercial	n/a	802(i) and 801(e)(1) See part V A and B	Yes	No	–
Biological Product	Partially processed biological product under section 351 of the PHSA	To be exported for further manufacture outside the U.S.	n/a	section 351(h) of the PHSA See part V A, B, and E	Yes	No	–
Device	Adulterated or Misbranded <u>BUT</u> complies with any applicable requirement of sections 514 and 515 of the Act, is not exempt from sections 514 or 515 of the Act by section 520(g) of the Act, and is not a banned device under section 516 of the Act	Either	n/a	801(e)(1) See part V A, B, and D	Yes	No	–
Device	Does not comply with an applicable requirement of sections 514 or 515 of the Act, is exempt from section 514 or 515 of the Act by section 520(g) of the Act, or is a banned device under section 516 of the Act	Commercial	Yes	802(b)(1) See part VII C and D	Yes	Yes	–

Type of Product	Status Under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act (PHSA)	Intended for Commercial Distribution or Investigational Use	Approved/ Legally Marketed in a Listed Country	Possible Export Provision Options and Relevant Guidance Document Chapter	Section 801(e)(1) applies?	Sections 802(f) and 802(g) apply?	Special Requirements
Device	Does not comply with an applicable requirement of sections 514 or 515 of the Act, is exempt from section 514 or 515 of the Act by section 520(g) of the Act, or is a banned device under section 516 of the Act	Investigational	n/a	802(c) See part VIII C	Yes	Yes, except for notification under (g)	A party may instead conduct the export and investigation pursuant to the requirements of 21 CFR Part 812
			Yes	802(b)(1) See parts VII C and D, VIII C	Yes	Yes	
Device	Does not comply with an applicable requirement of sections 514 or 515 of the Act, is exempt from section 514 or 515 of the Act by section 520(g) of the Act, or is a banned device under section 516 of the Act	Commercial, but exported to a listed country for further formulation, or processing, etc.	No, but exported in anticipation of market authorization	802(d) See part IX	Yes	Yes, except for notification under (g)	–
Device	Does not comply with an applicable requirement of sections 514 or 515 of the Act, is exempt from section 514 or 515 of the Act by section 520(g) of the Act, or is a banned device under section 516 of the Act	Either	n/a	801(e)(2) See part V D	Yes	No	Must submit request to FDA
Device	Does not comply with an applicable requirements of sections 514 or 515 of the Act, is exempt from section 514 or 515 of the Act by section 520(g) of the Act, or is a banned device under section 516 of the Act	Intended for use in a tropical disease or other disease not of significant prevalence in the U.S.	No	802(e) is an option for an export to an unlisted country if the product does not qualify for export under any other provision in section 802 of the Act See part X	Yes	Yes, except for notification under (g)	Requires approval of an application to FDA before the export can begin

Type of Product	Status Under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act (PHSA)	Intended for Commercial Distribution or Investigational Use	Approved/ Legally Marketed in a Listed Country	Possible Export Provision Options and Relevant Guidance Document Chapter	Section 801(e)(1) applies?	Sections 802(f) and 802(g) apply?	Special Requirements
Animal Drug or Feed	Adulterated or Misbranded	Either	n/a	801(e)(1) See part V A and B	Yes	No	If requires approval under section 512 of the Act and is banned in the United States, section 801(e)(3) of the Act prohibits export
Food or Cosmetic	Adulterated or Misbranded	n/a	n/a	801(e)(1) See part V A and B	Yes	No	–
Drug, Device, Biological Product, Animal Drug or Feed, Food, Cosmetic	In full compliance with the applicable Act or PHSA requirements for distribution and sale in the United States	Commercial	n/a	No specific export requirements	No	No	–

IV. Statutory Background

Some background information on the statutory requirements that existed before the enactment of the 1996 Amendments is helpful to understand why the 1996 Amendments were enacted.

A. Historical Background - Exports of Drugs and Biological Products That May Not be Sold in the United States

The Act's export provision originated in 1906 as part of the Federal Food and Drugs Act (Public Law 59-384). Section 2 of the 1906 Federal Food and Drugs Act stated that:

* * * no article shall be deemed misbranded or adulterated within the provisions of this act when intended for export to any foreign country and prepared or packed according to the specifications or directions of the foreign purchaser when no substance is used in the preparation or packing thereof in conflict with the laws of the foreign country to which said article is intended to be shipped; but if said article shall be in fact sold or offered for sale for domestic use or consumption, then this proviso shall not exempt said article from the operation of any of the other provisions of this act.

This export provision was included, with some modifications, in the Federal Food, Drug, and Cosmetic Act of 1938 (Public Law 75-717) where it was codified as section 801(d). Section 801(d) of the 1938 Act stated that:

A food, drug, device, or cosmetic intended for export shall not be deemed to be adulterated or misbranded under this Act 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 sold or offered for sale in domestic commerce

* * *

The 1938 act also defined the terms, “drug” and “new drug,” and these definitions led to the conclusion that section 801(d) of the 1938 Act did not apply to new drugs that did not comply with section 505 of the Act. (See, e.g., *United States v. An Article of Drug, etc* * * * *Ethionamide-INH*, No. 67 C 288 (E.D. N.Y. Aug. 19, 1967); *United States v. Yaron Laboratories, Inc.*, 365 F.Supp. 917, 919 (N.D. Cal. 1972); Compliance Policy Guide 7132c.01 (Oct. 1, 1980).) As a result, the Act was interpreted as permitting the export of approved drugs, but not permitting the export of unapproved new drugs. This interpretation was viewed as imposing hardships on the pharmaceutical industry (by impairing its ability to compete in international markets) without any accompanying public health benefits (see S. Rept. 99-225, 99th Cong., 2d sess. 5-6 (1985)).

To remedy the situation, Congress enacted the Drug Export Amendments Act of 1986 (Public Law 99-660). For human drug products and biological products, the 1986 Amendments created section 802 of the Act and established three separate “tracks” for exporting unapproved drugs and unlicensed biological products. Under “track 1,” FDA was authorized to approve an

application for the export of new human and animal drugs and biological products that were not approved in the United States, so long as the drug contained the same active ingredient(s) as a product for which marketing approval in the United States was being sought or the biological product was one for which licensing was actively being pursued. Exports under “track 1” were confined to 21 specific countries listed in section 802 of the Act. Those countries were: Australia, Austria, Belgium, Canada, Denmark, the Federal Republic of Germany, Finland, France, Iceland, Ireland, Italy, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.

Under “track 2,” FDA was authorized to approve the export of drugs and biological products intended for the treatment of tropical diseases. Persons seeking to export a drug under track 2 had to submit an application to FDA, and FDA had to find, based on “credible scientific evidence,” that the drug would be safe and effective in the country to which it would be exported in the prevention or treatment of a tropical disease in that country.

“Track 3” applied to partially processed biological products and amended section 351 of the PHS Act. FDA was authorized to approve the export of partially processed human biological products intended for further manufacture in any of the 21 listed countries, but the final product had to be approved or in the process of receiving approval from the foreign country.

Additionally, the 1986 Amendments added a new section 801(d) of the Act (regarding importation of drugs), and renumbered the existing section 801(d) as a new section 801(e)(1) of the Act.³

The 1986 Amendments, however, presented several problems and concerns. One significant problem was that the 1986 Amendments limited exports of most unapproved drugs and biological products to 21 countries. Although the 1986 Amendments provided criteria for adding more countries to the list, it omitted any administrative mechanism for doing so. Consequently,

³ The 1986 Amendments did not alter the export requirements for insulin and antibiotics. These products remained subject to the basic export requirements that are now in section 801(e)(1) of the Act because the products were subject to approval under provisions of the Act separate from section 505 of the Act and, as a result, exports could occur without prior FDA approval under section 802 of the Act.

exports of unapproved drugs and biological products to countries that were not on the list were not permitted.

The requirement that the drug contain the same active ingredient as a drug for which marketing approval in the United States was being “actively pursued” also caused some concern in the industry. Questions arose concerning the degree to which the active ingredient had to be the “same” or how “actively” the manufacturer had to be seeking approval.

The requirements in the 1986 Amendments for FDA approval before a product could be exported generated criticism and debate as well. The 1986 Amendments required a person to file an application to export a drug at least 90 days before the date on which the applicant proposed to export the drug, and required FDA to publish a notice in the *Federal Register* identifying the applicant, the drug to be exported, and the country to which the drug was being exported (for Track 1 exports only). The 1986 Amendments also established requirements for the application as well as the agency's action on an application. For example, if the agency decided to disapprove an application, it had to provide a written statement to the applicant describing deficiencies that the applicant must correct and give the applicant 60 days to correct those deficiencies. Some firms charged that this approval process took too long; others questioned why the United States should have to approve the export of a product to a foreign country, particularly when the foreign country had its own public health authorities or had approved the product for marketing.

B. Historical Background - Exports of Animal Drugs That May Not Be Sold in the United States

As stated earlier, section 801(e) of the Act was construed as not applying to the exportation of unapproved new human drugs. This interpretation also covered unapproved new animal drugs, and was made explicit in 1968 as part of the Animal Drug Amendments of 1968 (Public Law 90-399). Although the initial Congressional bill would have permitted exportation of unapproved new animal drugs, Congress, at the request of the then-Department of Health, Education, and Welfare, elected to amend section 801 of the Act to prevent the exportation of unapproved new animal drugs and animal feed containing unapproved new animal drugs (see S. Rept. 1308, 90th Cong., 2d Sess., 1968 U.S. Code Cong. & Admin. News 2160). The legislative history explained that the amendment’s purpose was to “preserve, essentially, the status quo with

respect to the export exemption” (id.).

The Drug Export Amendments Act of 1986 altered the export requirements for unapproved new animal drugs in the same manner that it changed the export requirements for unapproved new human drugs (such as limiting exports to 21 specific countries and requiring the exporter to be pursuing product approval in the United States as a condition for allowing exportation). Consequently, under the 1986 amendments, an unapproved new animal drug could be exported under section 802 of the Act.

C. Historical Background - Exports of Devices That May Not Be Sold in the United States

As stated earlier, then-section 801(d) of the Federal Food, Drug, and Cosmetic Act of 1938 (now codified at section 801(e) of the Act) stated that a food, drug, device, or cosmetic intended for export would not be considered adulterated or misbranded if the product: (1) Met the foreign purchaser’s specifications; (2) was not in conflict with the laws of the country to which it was being exported; (3) was labeled on the outside of the shipping package that the product was intended for export; and (4) was not sold or offered for sale in domestic commerce.

This authority remained unchanged until 1976 when, as part of the Medical Device Amendments Act of 1976 (Public Law 94-295), Congress amended the provision to state that the four criteria did not apply to any device that did not comply with an applicable requirement under sections 514 (performance standards) or 515 (premarket approval) of the Act, to devices that were exempt from sections 514 or 515 of the Act under section 520(g) of the Act (devices subject to an IDE), and to banned devices (under section 516 of the Act) *unless*, in addition to requiring compliance with section 801(e)(1) of the Act, the agency determined that exportation of the device would not be contrary to the public health and safety and the device had the approval of the foreign country that would receive the device. In other words, most unapproved devices could not be exported unless the agency determined that exportation would not be contrary to the public health or safety and that the foreign country approved of the device. This provision was, and remains, codified at section 801(e)(2) of the Act (21 U.S.C. 381(e)(2)).

As in the case of FDA drug export approvals, the statutory requirement that FDA approve device exports led to criticism from the device industry. The device industry criticized the agency

for the amount of time FDA took to determine whether an export request met the statutory criteria. FDA reduced the time for processing device export requests from an average of 91 days in 1992 to 10 days in 1995. Despite this significant reduction in processing time, the statute's export approval requirements were seen as adversely affecting the ability of U.S. firms to enter or to compete in foreign markets.

D. Enactment of the FDA Export Reform and Enhancement Act of 1996

The FDA Export Reform and Enhancement Act of 1996 (Public Law 104-134, and amended by Public Law 104-180) addressed the industries' chief problems and concerns. For human drugs and biological products that may not be sold in the United States, the 1996 Amendments:

- Amended section 801 of the Act to allow exports of approved drugs (except for insulin and antibiotics) to countries that have different or additional labeling requirements or conditions for use. The new provision, at section 801(f) of the Act, requires such drugs to be labeled in accordance with the requirements and conditions for use in the foreign country and also to be labeled in accordance with the Act. If the drug's labeling includes conditions for use that are not approved in the United States, the labeling must state that such conditions for use have not been approved under the Act.
- Replaced section 802 of the Act in its entirety with a new section 802 of the Act that:
 - Eliminated the requirement for prior FDA approval of exports of unapproved drugs in most cases,
 - Significantly expanded the list of countries to which unapproved products can be exported without prior FDA approval (and also provided administrative mechanisms for the Secretary of Health and Human Services (the Secretary) to add countries to the list and for FDA to permit exports of specific products to unlisted countries),
 - Authorized exports of unapproved drugs and biological products intended for use in clinical investigations in any of the listed countries,
 - Authorized the export of certain unapproved products to a listed country in anticipation of marketing approval in that country,

- Created a simple notification process for most exported products (as opposed to the application process required under the 1986 Amendments). Notification is *not* required for drugs exported for investigational use in a listed country or drugs exported to a listed country in anticipation of marketing authorization, and
- Authorized FDA to permit the export of unapproved products intended to treat tropical or other diseases that are “not of significant prevalence in the United States.”

For animal drugs that may not be sold in the United States, the 1996 Amendments:

- Restricted the authority to export an unapproved new animal drug to section 801(e)(1) of the Act. Animal drugs cannot be exported under section 802 of the Act because that section pertains to biological products, devices, and *human* drugs.
- The only unapproved new animal drugs that cannot be exported under section 801 of the Act are animal drugs that have been “banned in the United States” (see section 801(e)(3) of the Act).

For devices that may not be sold in the United States, the 1996 Amendments:

- Amended section 801 of the Act to permit exportation of certain devices under section 801(e) of the Act *or* under section 802 of the Act;
- Replaced section 802 of the Act in its entirety with a new section 802 of the Act that:
 - Eliminated the requirement for prior FDA approval for exports (for devices approved in a listed country or destined for clinical investigations in a listed country),
 - Created administrative mechanisms for the Secretary to add countries to the list and for FDA to approve exports of specific products to unlisted countries,
 - Authorized exports of unapproved devices intended for use in clinical investigations in any of the countries identified in section 802 of the Act,
 - Authorized the export of unapproved devices to a listed country in anticipation of marketing approval in that country,
 - Created a simple notification process for exported devices (as opposed to the application process under section 801(e)(2) of the Act). Notification is not required for devices exported for investigational use to a listed country or devices exported to a listed country in anticipation of marketing authorization in the listed country; and

- Authorized FDA to permit the export of unapproved devices intended to treat tropical diseases or other diseases that are “not of significant prevalence in the United States.”

This document describes the requirements for drugs (both human and animal), biological products, and devices under sections 801 and 802 of the Act and section 351(h) of the PHS Act, as amended by the 1996 Amendments. The general requirements under section 801(e)(1) of the Act also apply to exports of foods, cosmetics, antibiotics, and insulin that do not comply with the Act's requirements for sale and distribution in the United States. (The Act treats exports of antibiotics and insulin differently from other human drugs (see part VI of this guidance document).)

V. General Requirements for Products Exported Under Section 801(e)(1) of the Act

A. *Summary of Section 801(e)(1) of the Act*

Section 801(e)(1) of the Act contains general export requirements for any food, drug, device, or cosmetic that is adulterated or misbranded under the Act. These requirements also apply to products exported in accordance with sections 801(e)(2), 801(f), or 802 of the Act or section 351(h) of the PHS Act.⁴ Depending on the type of product being exported and the legal authority supporting the product's exportation, requirements in addition to those in section 801(e)(1) of the Act may apply. The 1996 Amendments made no changes to section 801(e)(1) of the Act.

Section 801(e)(1) of the Act states that a food, drug, device, or cosmetic intended for export shall not be deemed to be adulterated or misbranded if the article:

- Accords to the specifications of the foreign purchaser;
- Is not in conflict with the laws of the country to which it is intended for export;
- Is labeled on the outside of the shipping package that it is intended for export; and
- Is not sold or offered for sale in domestic commerce.

As a statutory exemption, this provision is to be construed narrowly. The party seeking to export the product bears the burden of demonstrating that the criteria of the exemption are met.

B. *Determining Compliance with Section 801(e)(1) of the Act*

During routine inspections, FDA will evaluate whether a firm has complied with section 801(e)(1) of the Act. Consequently, records are very important for demonstrating compliance

⁴ Section 802(f)(3) of the Act prohibits exportation of a product under section 802 of the Act if the requirements in section 801(e)(1)(A) through (e)(1)(D) of the Act are not met. The requirements in section 801(e)(1) of the Act also apply to partially processed biological products exported under section 351(h) of the PHS Act.

with each element of section 801(e)(1) of the Act. FDA's record keeping requirements that implement section 801(e)(1) of the Act can be found at 21 CFR § 1.101(b).

1. Meeting a Foreign Purchaser's Specifications

To demonstrate that the product meets the foreign purchaser's specifications, the firm exporting the product must maintain records which contain sufficient information to match the foreign purchaser's specifications to a particular export (see 21 CFR § 1.101(b)(1)). This could include details about the product (e.g., dosage strength, dosage form, purity, quality, operating parameters, composition, etc.) and any details concerning the product's manufacture (e.g., type of sterilization process to be used, compliance with a particular manufacturing standard, etc.) as requested by the foreign purchaser. For example, if the article is food with a food additive that is not approved in the United States, this could include records showing that the purchaser requested that the food contain the particular food additive. A second example would be records showing that the purchaser specifically requested the inclusion or exclusion of a particular manufacturing step, where the article is violative under U.S. cGMP's due to the presence or absence of that manufacturing step. A third example is where the foreign purchaser does not request a particular manufacturing step but instead requests that the product be manufactured pursuant to a set of specific manufacturing standards that are inconsistent with, or at least different from, U.S. cGMP's. In this example, sufficient records could include records showing that the purchaser requested that the product be manufactured pursuant to this set of manufacturing standards and that the manufacturing process met the specified standards. A fourth example is where the foreign purchaser places an order for a product but does not provide any specifications (e.g., that a particular food additive, manufacturing step, or manufacturing standard be used). In such a case, the foreign purchaser's order, standing alone, would not be sufficient to satisfy section 801(e)(1)(A) of the Act.

In addition, if the foreign purchaser sought 5,000 bottles of drug X tablets, with each tablet at a 50 mg. dose, FDA would look for records to show that a particular shipment of drug X to the foreign purchaser consisted of 5,000 bottles of drug X in a 50 mg. tablet form. As noted in the preamble to the final rule (66 FR 65429 (December 19, 2001)), records stating only that drug

X was shipped to the foreign purchaser would not be satisfactory because the records would not reflect whether the purchaser sought a particular dosage or quantity and would not show whether the export met that dosage specification or whether the quantity that was exported met the purchaser's specification.

FDA does not expect complete specifications to accompany every order of the same product. For example, if an exporter signs a contract to ship the same item to a foreign purchaser on a monthly basis, the agency would not expect the exporter to obtain complete specifications for each monthly shipment. However, FDA would expect the exporter to have specifications that applied to the initial shipment and records showing that subsequent shipments correspond to the same initial specifications. The agency's principal interest is to link records to specific export shipments to verify that a particular exported product met the foreign purchaser's specifications. The level of detail in the specifications may vary between orders, but § 1.101(b)(1) requires exporters to maintain records that demonstrate that the exported product met the foreign purchaser's specifications.

FDA recommends that the firm have an English-language translation of the specifications document or be prepared to translate the document into English at the time of any FDA inspection.

2. Not in Conflict with the Laws of the Importing Country

Under 21 CFR § 1.101(b)(2), there are two possible ways for demonstrating that the product to be exported does not conflict with the laws of the importing country. The regulation states that records demonstrating that the product does not conflict with the laws of the importing country may consist of either:

- a letter from an appropriate foreign government agency, department, or other authorized body stating that the product has marketing approval from the foreign government or does not conflict with that country's laws, or
- a notarized certification by a responsible company official in the United States that the product does not conflict with the laws of the importing country. If a certification is used, the certification must be in English and include a statement

acknowledging that the person making the certification is subject to the provisions of Title 18, section 1001 of the United States Code.⁵

On July 22, 2002, FDA stated, in response to a petition for reconsideration, that it will generally not take enforcement action regarding § 1.101(b)(2) while the agency considers whether any changes are necessary to the regulatory provision as to how a company can demonstrate that the product to be exported does not conflict with the laws of the importing country. FDA's July 22, 2002, letter also stated "we reiterate that affected parties must continue to comply with the statutory requirements for exports under sections 801(e) and 802 of the Act." On June 1, 2004, FDA published an advance notice of proposed rulemaking seeking comments on this issue (69 FR 30842).

3. Shipping Package Labeling Showing That the Product Is Intended for Export

To demonstrate that the product is labeled on the outside of the shipping package that it is intended for export, § 1.101(b)(3) requires records that show such labeling or labeling statements. These records may consist of copies of labels or labeling statements, such as "For export only," that are placed on shipping packages or, if the exported product lacks a shipping package or container, on shipping invoices or other documents accompanying the exported product.

4. Product Is Not Sold or Offered for Sale in the United States

To demonstrate that the product is not sold or offered for sale in the United States, § 1.101(b)(4) indicates that production and shipping records for the exported product and promotional materials may be sufficient.

For example, in situations where there are multiple batches of the same product, batches of a product that are intended for export throughout the manufacturing process or produced on manufacturing lines that are dedicated to export markets *may* meet the requirement in section 801(e)(1)(D) of the Act. Even in these situations, however, if a firm is selling the same product

⁵ Under 18 U.S.C. 1001, it is a criminal offense to knowingly and willfully submit false information to the government.

both in the United States and overseas and the product for sale in the United States is adulterated or misbranded in the same way as the product intended for export, then the agency would consider the product to be sold or offered for sale in domestic commerce. Another situation is where a firm does not decide to export a specific product until it has already begun the manufacturing process, for example to meet an overseas inventory need. This also may meet the section 801(e)(1)(D) requirement if the decision to export the product is made at a distinct, identifiable, and documented point in the manufacturing process; the product is not adulterated or misbranded at the point the decision is made; and the action that causes the product to become adulterated or misbranded, such as conforming the product to a foreign specification, is taken subsequent to the decision. In each of these situations, the product intended for export should be clearly identifiable and segregable from product intended for the U.S. market.

If the product's sale in the United States does not violate the Act, and the same product is intended for export for the same approved use and is accompanied closely by the FDA-approved labeling (if FDA labeling approval is required), FDA may consider the product to be sold or offered for sale in the United States. Nonetheless, under these circumstances, FDA would consider the product to be in compliance with the Act such that it would *not* have to meet the criteria of section 801(e)(1) of the Act to be exported. By stating that the product is “accompanied closely” by the FDA-approved label (if FDA is required to approve the product’s labeling), FDA does not expect the FDA-approved label be affixed to each exported product, but the agency does expect the FDA-approved label to be included in the export shipment. The agency recognizes that no interest would be served by requiring firms to attach FDA-approved labels to exported products otherwise in compliance with the Act’s requirements for sale and distribution in the United States if those labels would have to be removed or altered for the product to be sold in a foreign country. In contrast, if the product to be exported:

- involves a use that is not approved in the United States, or
- is labeled solely in a foreign language and that foreign language labeling discusses uses that have not been approved by FDA,

then the product is “unapproved” and falls within the Act’s export provisions. In these cases, FDA would not consider the product with the foreign language label to be sold or offered for sale in the

United States within the meaning of section 801(e)(1)(D) of the Act unless this version of the product, with the foreign language label, was sold or offered for sale in the United States.

To summarize, the requirements in section 801(e)(1) of the Act apply to foods, drugs (both human and animal (except for “banned” animal drugs, which may not be exported)), biological products, devices, and cosmetics intended for export, whether they are exported under section 801 or section 802 of the Act or section 351(h) of the PHS Act. Furthermore, depending on the type of product being exported and the legal authority supporting the product’s exportation, additional requirements may apply.

C. Special Restrictions on Animal Drugs

The 1996 Amendments excluded certain animal drugs from exportation. Section 801(e)(3) of the Act states that animal drugs that have been “banned in the United States” may not be exported. Neither the 1996 Amendments nor the legislative history explains what constitutes a “banned” animal drug.

D. Special Requirements for Certain Devices

Some devices have additional statutory requirements before they can be exported under section 801(e)(1) of the Act. Under section 801(e)(2) of the Act, if a device:

- Does not comply with an applicable requirement under sections 514 (performance standards) or 515 (premarket approval) of the Act,
- is exempt from either such section under section 520(g) of the Act, or
- is a banned device under section 516 of the Act,

the device may not be exported *unless*, in addition to the requirements in section 801(e)(1) of the Act, FDA has determined that device’s exportation is not contrary to the public health and safety and has the approval of the country to which it is intended for export, or the device is eligible for export under section 802 of the Act.

The Act provides that any device introduced into interstate commerce after May 28, 1976, is automatically considered to be a “class III” device requiring premarket approval under section 515 of the Act. Such devices may not be legally marketed unless and until FDA: (1) Classifies the

device into class I or II; (2) grants marketing clearance by issuing an order under section 513(i) of the Act, in response to a report submitted by the sponsor under section 510(k) of the Act, determining that the device is substantially equivalent to a predicate device that does not require premarket approval (hereinafter referred to as 510(k) marketing clearance); or (3) issues an order under section 515(d)(1)(A) of the Act approving an application for premarket approval.

The Act prohibits exportation of class III devices requiring premarket approval unless the criteria under section 801(e)(2) of the Act are met (or the device qualifies for export under section 802 of the Act). FDA has exercised its enforcement discretion and, to date, has not taken enforcement action against a firm who has not complied with the export criteria in section 801(e)(2) of the Act, *provided* that the firm has reasonably concluded that FDA would have granted 510(k) marketing clearance if a report under section 510(k) of the Act had been submitted. FDA intends, on a case by case basis, to continue to consider the exercise of its enforcement discretion in this manner with respect to the requirements in section 801(e)(2) of the Act. FDA emphasizes, however, even if a firm reasonably believes that its device would receive a 510(k) marketing clearance, FDA does not intend to consider the exercise of its enforcement discretion in this manner with respect to the requirements in section 801(e)(1) of the Act.

To help FDA determine whether exportation of the device is not contrary to the public health and safety, FDA recommends that firms provide basic safety data for the device. Such data often consists of a statement certifying that a search of medical databases has not identified any adverse safety data for similar devices or the materials used in the device, or summaries of any adverse safety data, including a discussion as to why the adverse effects should not be considered applicable to the device that is to be exported. Brief summaries of available animal safety studies conducted with the device and safety data from human clinical studies are also helpful. For in vitro diagnostic devices, where the device is to be the sole determinate of whether a particular course of treatment will be initiated for a life-threatening disease, the agency recommends that the firm provide a statement indicating whether an alternative test will be available to confirm the test results. FDA ordinarily does not need safety data if the device is the subject of an approved IDE or is considered to have an approved IDE, and will be marketed or used in the importing country

for the same intended use.⁶

To help FDA determine whether exportation of the device has the approval of the country to which it is intended for export, FDA recommends that the firm obtain a letter from the foreign country authorizing the device's importation. If the firm is exporting the device to a country in the European Economic Area and the device has received a CE mark, documentation of the CE mark will ordinarily be sufficient.

Additional information regarding device exports under section 801(e)(2) of the Act can be found in the guidance document entitled, "Procedures for Obtaining FDA Approval to Export Unapproved Medical Devices." (To obtain copies of this guidance, see "For Further Information Contact" in part XII of this document.)

E. Special Requirements for Partially Processed Biological Products

The 1996 Amendments also changed the export requirements for partially processed biological products. Under section 351(h) of the PHS Act, a partially processed biological product may be exported if it is:

- "Not in a form applicable to the prevention, treatment, or cure of diseases or injuries of man,"
- not intended for sale in the United States, and
- intended for further manufacture into final dosage forms outside the United States.

Exports of such products must comply with section 801(e)(1) of the Act and with cGMP's or international manufacturing standards as certified by an international standards organization recognized by the agency.

1. What Constitutes a Partially Processed Biological Product?

FDA interprets the term "partially processed biological products" as meaning biological products requiring purification, inactivation, fractionation, or significant chemical modification

⁶ A device may be considered to have an approved IDE if an institutional review board determines that the device is a non significant risk device, and provided the device has met the requirements for non significant risk devices under 21 CFR § 812.2(b).

(such as the formation or breakage of covalent bonds and the incorporation of peptides into a diagnostic test kit) before being used in the formulation of a final product. Thus, a finished bulk product that could be formulated into a finished dosage form through manufacturing steps other than purification, inactivation, fractionation, or significant chemical modification would not constitute a partially processed biological product that could be exported under section 351(h) of the PHS Act. Certain other products, such as source plasma and source leukocytes, also would not be partially processed biological products because they are finished products (notwithstanding the possibility that their intended use may be as a source material for further manufacturing into another product), and would be subject to licensure if distributed in the United States. Note that unlicensed biological products that do not qualify for export under section 351(h) of the PHS Act may qualify for export under section 802 of the Act.

Products that do qualify as partially processed biological products include intermediate biological products that a firm has partially processed and that would be subject to licensure as final products after the completion of additional manufacturing steps. FDA encourages persons who may be uncertain as to whether their products are partially processed biological products to contact the Center for Biologics Evaluation and Research (see the “For Further Information Contact” in part XII of this document for the address and phone number).

2. cGMP Requirements

Section 351(h) of the PHS Act also requires partially processed biological products to be “manufactured, processed, packaged, and held in conformity with current good manufacturing practice requirements” or meet international manufacturing standards recognized by the agency. FDA inspects firms to ensure that they are in compliance with cGMP’s.

Section 351(h) of the PHS Act refers to “international manufacturing standards as certified by an international standards organization” recognized by FDA. As of August, 2006, FDA has not recognized any such international standards organizations for purposes of section 351(h) of the PHS Act.

3. Additional Requirements Under Section 351(h) of the PHS Act

All exports of FDA-regulated products that may not be sold or marketed in the United States, including partially processed biological products exported under section 351(h) of the PHS Act, must conform to the standard export requirements of section 801(e)(1) of the Act. Thus, a product intended for export under section 351(h) of the PHS Act must:

- Accord with specifications of the foreign purchaser;
- not be in conflict with the laws of the country to which it is intended for export;
- be labeled on the outside of the shipping package that it is intended for export; and
- not be sold or offered for sale in domestic commerce.

Consistent with section 801(e)(1) of the Act, section 351(h)(2) of the PHS Act further requires that the product may not be intended for sale in the United States.

Records are important in FDA's evaluation of compliance with section 351(h) of the PHS Act, including the requirements section 801(e)(1) of the Act. FDA regulations, at 21 CFR 1.101(c), require persons exporting a partially processed biological product under section 351(h) of the PHS Act to meet the recordkeeping requirements in § 1.101(b) (discussed in part V.B above) and to maintain the following records:

- Records demonstrating that the product for export qualifies as a partially processed biological product and not in a form applicable to the prevention, treatment, or cure of diseases or injuries of man;
- Records demonstrating that the partially processed biological product was manufactured in accordance with cGMP's;
- Records demonstrating the distribution of the exported, partially processed biological products;
- Copies of all labeling that accompanies the exported, partially processed biological product; and
- Other records demonstrating that the product is intended for further manufacture into a final dosage form outside the United States. This may include a container label with the statement, "Caution: For Further Manufacturing Use Only" and any package insert.

Additionally, firms that manufacture, prepare, or process partially processed biological products for export must register with FDA and list their products under section 510 of the Act and

21 CFR parts 207, 607, or 807, whichever is applicable.

VI. Labeling Requirements for Drugs and Biological Products Exported Under Section 801(e)(1) of the Act - Section 801(f) of the Act

The 1996 Amendments contained a new provision that permits the export of drugs (other than insulin, antibiotics, animal drugs, or drugs exported under section 802 of the Act)⁷ that may be sold in the United States and are being exported to a country that has different or additional labeling requirements or conditions for use (compared to those on the FDA-approved labeling), and the foreign country requires the drug to be labeled in accordance with those requirements or uses. For these drugs, section 801(f) of the Act imposes certain labeling requirements. Under section 801(f)(1) of the Act, the drug intended for export may be labeled in accordance with the foreign requirements and conditions for use *as long as* the drug is also labeled in accordance with the Act.

If the labeling includes conditions of use that are not approved in the United States, section 801(f)(2) of the Act requires the labeling to state that those uses are not approved under the Act. The Act defines “labeling” as “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.” Thus, to comply with section 801(f)(2) of the Act, FDA suggests that a firm place a statement on the labeling regarding the uses that are not approved in the United States wherever an unapproved use appears. For example, if an unapproved use is on the immediate label and on the product’s container, a statement identifying the uses that are not approved in the United States would appear on the immediate label and on the product’s container.

FDA has received questions regarding whether the statement identifying the uses that are not approved in the United States should be in the language used in the foreign country. Although

⁷ Insulin and antibiotics are excluded from section 801(f) of the Act because they historically have been subject only to the export requirements now seen in section 801(e)(1) of the Act. In 1997, the Food and Drug Administration Modernization Act (Public Law 105-115) repealed the separate approval provisions for these products and, as a result, made them subject to section 505 of the Act. In order to permit insulin and antibiotics to continue to be exported under section 801(e)(1), the 1997 legislation expressly stated that insulin and antibiotics may be exported without regard to the requirements in section 802 of the Act so long as they meet the export requirements in section 801(e)(1) of the Act. See section 802(i) of the Act.

section 801(f) of the Act is silent on this point, the agency suggests that the statement be in the language used in the foreign country (i.e., the language of the foreign use labeling as a whole) because the statutory requirement is more meaningful if foreign consumers can read the statement.

In some instances, products that may be exported in compliance with the labeling requirements in section 801(f) of the Act may also qualify for export under section 802(b)(1)(A) of the Act (discussed in part VII.D of this document). In such cases, a firm may elect to export a product under either section 801(e) or section 802(b) of the Act so long as the product meets the statutory requirements for export. A drug exported under section 802 of the Act is *not* subject to the labeling requirements in section 801(f) of the Act.

VII. Exports of Unapproved Drugs, Biological Products, and Devices Under Section 802(b) of the Act

A. *Drugs and Biological Products*

As stated earlier, courts and FDA have interpreted section 801(e) of the Act as being inapplicable to unapproved new drugs and biological products. As a result, the 1986 Amendments amended the Act so that the export of unapproved new drugs and biological products was regulated under section 802 of the Act.

The 1996 Amendments, insofar as human drugs and biological products are concerned, modified the scope of section 802 of the Act to state that the provision applies to drugs and biological products that:

- Require approval under section 505 of the Act or, for biological products, require licensing under section 351 of the PHS Act;
- do not have such approval or license; and
- are not exempt from section 505 of the Act or section 351 of the PHS Act.

Thus, section 802 of the Act applies to unapproved new human drugs and biological products and to approved human drugs and biological products being exported for unapproved uses.⁸ This includes a drug required to have approval under section 505 of the Act and lacking such approval, a drug that does not comply with its conditions of approval, and a drug that does not comply with an applicable over-the-counter drug monograph. If FDA disapproves an application for a drug or biological product, and that product has been or will be exported to one or more foreign countries, section 802(a) of the Act requires FDA to notify the appropriate foreign public health official in those countries of its decision.

Section 802 of the Act also contains special provisions for drugs and biological products intended for investigational use in a listed country, drugs and biological products intended for

⁸ Insulin and antibiotics may be exported without regard to the requirements of section 802 of the Act if they meet the requirements in section 801(e)(1) of the Act. See section 802(i) of the Act and footnote 7, above.

further processing or labeling to fill the pipeline in anticipation of marketing authorization in a listed country, and drugs and biological products intended to treat a tropical disease or disease that is “not of significant prevalence in the United States.” These provisions are discussed in parts VIII through X of this document.

B. Devices

Section 802(b) of the Act, like section 801(e)(2) of the Act, applies to devices that:

- Do not comply with an applicable requirement under section 514 or 515 of the Act;
- are subject to an IDE; or
- are banned devices.

This means that devices that have premarket approval are *not* subject to section 802 of the Act, nor are devices that are the subject of a marketing clearance under the premarket notification provision under section 510(k) of the Act. As is the case for disapproved drugs and biological products, if FDA disapproves an application for premarket approval under section 515 of the Act, and the device has been or will be exported to one or more foreign countries, section 802(a) of the Act requires FDA to notify the appropriate foreign public health official in those countries of its decision.

Section 802’s provisions for products intended for investigational use in a listed country, intended for further processing or labeling to fill the pipeline in anticipation of marketing authorization in a listed country, or intended to treat a tropical disease or disease that is “not of significant prevalence in the United States” also apply to devices.

C. Basic Requirements for All Products Exported Under Section 802 of the Act

Section 802(f) of the Act imposes certain basic requirements for all drugs, biological products, and devices exported under section 802 of the Act. In brief, these requirements are as follows:

- The product must be manufactured, processed, packaged, and held in “substantial conformity” with cGMP’s or meet international standards as certified by an international standards organization recognized by FDA. Neither the 1996

Amendments nor its legislative history explains what constitutes “substantial conformity” with cGMP’s, but the legislative history for the Generic Drug Enforcement Act of 1992 may be instructive. In discussing the terms “substantial compliance” with cGMP’s and good laboratory practices, the House Committee on Energy and Commerce suggested that “substantial compliance” could not mean *full* compliance with GMPs because FDA “lacks the continuing presence that would be necessary to conclude that a firm is in full compliance with GMPs and GLPs” (see H. Rept. 102-272, 102d Cong., 2d sess. 20 (1992)). FDA interprets the term “substantial conformity” under section 802(f)(1) of the Act in a similar manner. The term does mean that the firm should have passed its most recent GMP inspection (or that GMP violations have been rectified, and the firm has credible systems and personnel in place to prevent a recurrence of the violation(s)). The agency has not recognized an international standards organization for purposes of section 802(f) of the Act, but is examining this issue closely.

- The product must not consist in whole or in part of any filthy, putrid, or decomposed substance and must not have been prepared, packed or held under insanitary conditions where it may have been contaminated with filth or whereby it may have been rendered injurious to health;
- The container for the product must not be composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health;
- The product must have the strength, purity, and quality that it purports or is represented to possess;
- For drugs, no substance may be mixed or packed with the drug that would reduce the drug’s quality or strength or may substitute in whole or in part for another substance in the drug;
- The product must comply with the requirements in section 801(e)(1) of the Act. (A discussion of the requirements in section 801(e)(1) of the Act appears in part V.B of this guidance document. FDA regulations, at 21 CFR 1.101(b), describe the records

that a person must retain to demonstrate compliance with section 801(e)(1) of the Act.)

- The product cannot be the subject of a notice by FDA or the U.S. Department of Agriculture determining that the probability of reimportation of the exported product would present an imminent hazard to the public health and safety of the United States, such that exportation must be prohibited;
- The product cannot present an imminent hazard to the public health of the country to which it would be exported; and
- The product must be labeled in accordance with the requirements and conditions of use in the listed country (see part VII.D., below) in which it received valid marketing authorization, if applicable, and the country to which it would be exported, and must be labeled in the language and units of measurement used in or designated by the country to which the drug or device would be exported.

Additionally, a product may not be exported if it is not promoted in accordance with these labeling requirements.

If the above requirements are not met, section 802(f) of the Act states that the drug or device may not be exported under section 802 of the Act. Furthermore, in determining whether a drug or device may present an imminent hazard to the public health of the foreign country or is improperly labeled or promoted, section 802(f) of the Act requires FDA to consult with the “appropriate public health official in the affected country.”

Exporters are responsible for determining whether export is permitted under the Act and whether their exports meet the requirements in section 802(f) of the Act. During an inspection, FDA will evaluate compliance with the relevant export provisions as appropriate. As discussed below, section 802(g) of the Act requires persons exporting drugs and devices under section 802(b)(1) of the Act to maintain records of such exported products and the countries to which they were exported and to provide a simple notification to the agency regarding such exports. FDA’s export notification requirements can be found at 21 CFR 1.101(d).

*D. Exports of Unapproved New Drugs, Biological Products, and Devices
to a Listed Country - Section 802(b)(1)(A) of the Act*

The principal provision authorizing the exportation of unapproved new drugs, biological products, and devices is section 802(b)(1)(A) of the Act. Section 802(b)(1)(A) of the Act states that a drug or device “may be exported to any country, if the drug or device complies with the laws of that country and has valid marketing authorization by the appropriate authority” in Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or any member nation in the European Union or the European Economic Area. As of July, 2007, the EU countries are: Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom. The EEA countries are the EU countries, Iceland, Liechtenstein, and Norway. The number of “listed countries” expands automatically as countries become members of the EU or the EEA.

This means that a firm whose drug or device has received marketing authorization in *any* of the countries listed above can export that drug or device to *any* country in the world, without submitting an export request to FDA or receiving FDA approval to export the drug or device, as long as the drug or device meets applicable requirements of the Act, including the laws of the country to which the product is being exported. This is a change from the 1986 Amendments, under which firms had to seek prior FDA approval to export under this provision.

FDA interprets the term “valid marketing authorization” as meaning an affirmative decision by the appropriate public health authority in a foreign country to permit the drug, biological product, or device to be sold in that country. For example, under this interpretation, if country D approves a drug for investigational use, the approval would not constitute “valid marketing authorization” because country D’s decision did not extend to commercial marketing. Likewise, a decision by country D to permit sales to another country would not represent “valid marketing authorization” because it does not permit sales within country D.

Some countries, however, have regulatory systems that permit marketing without an affirmative act or decision by the government. In such cases, FDA may consider a drug, biological product, or device to have “valid marketing authorization” if the listed country does not object to

the product's marketing in that country. In these cases, FDA recommends that the firm obtain a document from the relevant authority in the listed country indicating that it does not object to the product's marketing.

As for the word "drug," the drug to be exported under section 802(b)(1)(A) of the Act should be the same product as the drug that received marketing authorization in the listed foreign country. Thus, the issue of whether the drug to be exported must be exactly *identical* to the drug authorized in the listed country may depend on the conditions surrounding market authorization in the foreign country. For example, under this interpretation, if country E's marketing authorization applies only to a drug product with a specific composition, rather than to drugs that have a particular active ingredient or general composition, then the drug that is to be exported from the United States should have the same composition as the drug that received marketing authorization in country E. If, however, country E approves a drug product and, as a result of that approval, permits marketing of other drugs using the same active ingredient, then the "drug" that could be exported under section 802(b)(1)(A) of the Act could be any drug that has the same active ingredient.

Similarly, the product's *use* can be an issue. If the listed country approved the drug for a specific use, then the exported drug should be indicated for that specific approved use. For example, under this interpretation, if country E grants market authorization for a drug only to treat disease X, then a drug exported under section 802(b)(1)(A) of the Act in reliance on country E's marketing authorization should be indicated for treatment only of disease X. If, however, the listed country's market authorization is not specific to a particular use, then the exported drug can be for any use, provided that such use remains consistent with the terms of the listed country's market authorization.

Similar concepts apply to devices. Devices that are exported under section 802(b)(1)(A) of the Act should be similar (to the degree that any variation could not affect the safety or effectiveness of the product) or identical to the devices that receive marketing authorization in a listed country, depending on the requirements of that listed country. The uses for the exported device should also be consistent with the requirements of the listed country.

E. Expanding the List of Countries in Section 802(b)(1)(A) of the Act

The list of countries in section 802(b)(1)(A) of the Act can expand. The 1996 Amendments contained a mechanism whereby the Secretary may add other countries to the list, provided that the country meets certain criteria. These criteria include: (1) Statutory or regulatory requirements which require the review of drugs and devices for safety and effectiveness by a government entity in that country and which authorizes marketing approval of only those drugs and devices that trained and qualified experts acting on behalf of the government have determined to be safe and effective, (2) statutory or regulatory requirements pertaining to cGMPs, (3) statutory or regulatory requirements for reporting adverse events and for removing unsafe or ineffective drugs and devices from the market, (4) statutory or regulatory requirements that a product's labeling and promotion be in accordance with the product's approval, and (5) equivalence of the country's marketing authorization system with that in the listed countries.

Under section 802(b)(1)(B) of the Act, the authority to add countries to the list rests solely in the Secretary of Health and Human Services. Thus, FDA has no authority to add countries to the list.

*F. Exports of Unapproved New Drugs and Biological Products to an Unlisted Country -
Section 802(b)(2) and (b)(3) of the Act*

If a firm intends to export an unapproved new drug (including a biological product) to a foreign country not included in section 802(b)(1)(A) of the Act and the drug does not have valid marketing authorization in a listed country, the firm has two other options for exporting the product.⁹

One option is in section 802(b)(2) of the Act. This section permits a firm to export an unapproved drug directly to an unlisted country if:

- The drug complies with the laws of the foreign country and has valid marketing

⁹ The provisions of sections 802(b)(2) and (b)(3) of the Act do *not* apply to devices. Congress omitted devices from these provisions because it found FDA's practice of permitting, under section 801(e)(2) of the Act, exports of devices that had approved IDE's to be an acceptable alternative.

authorization by the “responsible authority” in that country, and

- FDA determines that the foreign country has statutory or regulatory requirements:
 - Which require the review of drugs for safety and effectiveness by a government entity in that country and which authorize marketing 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 determination on adequate and well-controlled investigations (including clinical investigations);
 - pertaining to cGMP’s;
 - for reporting adverse events and for removing unsafe or ineffective drugs from the market; and
 - which require that the labeling and promotion be in accordance with the product’s approval.

FDA recommends that firms intending to export drugs under section 802(b)(2) of the Act provide to the agency documentation showing that the drug complies with the foreign country’s laws and has valid marketing authorization. (If the country has a regulatory system that allows marketing without an affirmative decision by the government, FDA recommends that the firm obtain a document indicating that the authorities in that country do not object to the product’s marketing.) The agency also suggests that firms provide documentation so FDA can make its determination on the foreign country’s statutory and/or regulatory requirements. Copies of the foreign country’s laws and regulations (in English) may be helpful, but are not required; firms may also provide a description of the foreign country’s laws and regulations with citations that identify the precise law or regulation. If FDA cannot make the necessary determinations concerning the foreign country’s statutory and regulatory requirements, the firm cannot export the drug under section 802(b)(2) of the Act.

Because section 802(b)(2) of the Act requires FDA to evaluate the foreign country’s statutory and regulatory system, the agency’s determination concerning the foreign country’s statutory and regulatory requirements may be applicable to subsequent exports if the foreign country’s statutes or regulations remain unchanged. FDA intends to make decisions under section

802(b)(2) publicly available, either through a notice in the *Federal Register* or through some other means.

The second option is in section 802(b)(3) of the Act. This section permits a firm to petition the agency to authorize exportation to an unlisted country if the conditions for export under section 802(b)(1) and 802(b)(2) of the Act cannot be met. Under section 802(b)(3) of the Act, FDA shall allow exportation of the drug if:

- The person exporting the drug: (1) Certifies that the drug would not meet the conditions for approval under the Act or the conditions for approval in a listed country; and (2) provides “credible scientific evidence” for the product to be exported that is acceptable to FDA to show that the drug would be safe and effective under the conditions of use in the country to which it is being exported. The statute does not specify what constitutes “credible scientific evidence,” but an adequate and well-controlled study or studies, animal and in vitro pharmacology and toxicology studies, microbiology studies (for biological products), and statistical analyses of data should be helpful; and
- the appropriate health authority in the foreign country that is to receive the drug: (1) Requests approval of the drug’s exportation; (2) certifies that the health authority understands that the drug is not approved under the Act or by any listed country; and (3) concurs that the scientific evidence provided to FDA is credible scientific evidence that the drug would be reasonably safe and effective in the foreign country. Please note that the foreign health authority must “concur” that the evidence provided to FDA is credible scientific evidence regarding the drug’s safety and efficacy; this means that the foreign health authority should base its concurrence on the same evidence presented to FDA. If the foreign health authority reviewed different evidence or if FDA cannot determine whether the foreign health authority reviewed or concurred with the same evidence, then the requirement in section 802(b)(3) of the Act has not been met. Similarly, FDA has received requests under section 802(b)(3) of the Act where the requesting party states that the foreign government “does not object” to the product’s importation; the foreign

government's acquiescence to importation does not satisfy section 802(b)(3) of the Act's requirement that the foreign government concur that the scientific evidence provided to FDA is credible scientific evidence of the drug's safety and effectiveness. A letter from the relevant foreign government entity addressing each item in this paragraph will, in most circumstances, be acceptable.

Exports under section 802(b)(3) of the Act, therefore, differ from exports under section 802(b)(2) of the Act in two important respects: (1) Exports under section 802(b)(3) of the Act involve the submission of scientific evidence to FDA and to foreign health authorities; and (2) exports under section 802(b)(3) of the Act are situation-specific (i.e., they pertain to a specific drug intended for export to a specific country).

Because of these differences, a decision to allow exports of a particular drug under section 802(b)(3) of the Act does not extend to other drugs. Section 802(b)(3) of the Act requires a person to provide FDA with "credible scientific evidence" that the drug will be safe and effective under the conditions of use in the foreign country, and the foreign country must concur that the scientific evidence provided to FDA is credible scientific evidence that the drug would be reasonably safe and effective. However, because drug products may differ in formulation, dosage, route of administration, or other respects, scientific evidence to show that one drug is safe and effective may not necessarily show that another drug, made by a different firm or even the same firm, is safe and effective. As a result, the Act's emphasis on providing and reviewing credible scientific evidence will, in most cases, prevent a person from relying on an earlier decision to allow exportation under section 802(b)(3) of the Act.

FDA has 60 days to act on a request to export a drug under section 802(b)(3) of the Act. The agency plans to begin the 60 day period on the date that it receives a *complete* petition containing the certification and evidence required by the Act. Please note, however, that while FDA tries to act on export requests expeditiously, the Act does *not* allow exportation to proceed if FDA has not responded within 60 days.

As a reminder, any person who exports a drug under section 802 of the Act also must comply with the basic export requirements set forth in section 802(f) of the Act and with the recordkeeping requirements in section 802(g) of the Act.

Persons who wish to export a drug under sections 802(b)(2) or 802(b)(3) of the Act should address any questions to, and send their documentation or requests to:

(For Biological Products)

Division of Case Management (HFM-610),
Center for Biologics Evaluation and Research,
Food and Drug Administration,
1401 Rockville Pike, Suite 200N,
Rockville, MD 20852-1448.

(For Drug Products)

Executive Secretariat Team (HFD-6),
Center for Drug Evaluation and Research,
1451 Rockville Pike,
Rockville, MD 20852-1420.

VIII. Exports of Unapproved Drugs and Devices for Investigational Use to Listed Countries Under Section 802(c) of the Act

A. *Historical Background*

The 1986 Amendments did not impose any special requirements for drugs or devices exported for investigational use. Moreover, FDA did not apply section 801(e) of the Act to investigational drugs because courts had interpreted section 801 of the Act as not applying to “new drugs.” As a result, FDA regulated the exportation of unapproved new drugs (including biological products) for investigational use under its authority over investigational drugs at section 505(i) of the Act.

FDA issued regulations governing the exportation of unapproved new drugs for investigational use on January 18, 1984 (49 FR 2095), with minor modifications between 1984 and 2002. These regulations were codified at 21 CFR § 312.110, and so the program became known as the “312 program.” The regulations required any person who intends to export an unapproved new drug product for use in a clinical investigation either to have an IND or to submit a written request to FDA. The regulations required the written request to provide sufficient information about the drug to satisfy FDA that the drug is appropriate for investigational use in humans, that the drug will be used for investigational purposes only, and that the drug may be legally used by the consignee in the importing country for the proposed investigational use. The regulations further stated that the request must specify the quantity of the drug to be shipped and the frequency of expected shipments. If FDA authorized exportation of the drug, it would notify the government of the importing country. The regulations, however, did not apply to drugs approved for export under section 802 of the Act or section 351(h)(1)(A) of the PHS Act. As discussed in part VIII.B., below, the agency recently issued a final rule to modify the regulations for the 312 program.

In contrast, the agency did apply section 801(e) of the Act to investigational devices. This was partly because, unlike the situation for drugs, the Act contains only one definition for “device.” The agency issued a regulation on device exports on January 18, 1980 (45 FR 3732 at 3751). The provision, codified at § 812.18(b), simply stated that a person who intends to export an unapproved device must obtain FDA approval (under what is now part of section 801(e)(2) of the Act) before exporting the device.

B. Impact of the 1996 Amendments on Drugs Exported for Investigational Use

The 1996 Amendments impacted the 312 program significantly by creating a new section 802(c) of the Act. In brief, section 802(c) of the Act permits a firm to export an unapproved drug for investigational use in any of the *listed* countries without prior FDA approval or even an IND. The only requirements are that the drug be exported in accordance with the laws of the foreign country and comply with the basic export requirements in section 802(f) of the Act. The exporter, under section 802(g) of the Act, must also maintain records of all drugs exported and the countries to which they were exported.

It is important to note that section 802(c) of the Act allows exports of drugs and devices “intended for investigational use *in any [listed] country...in accordance with the laws of that country*” (emphasis added). The key statutory phrase is that the drug or device must be intended for investigational use *in a listed* country. FDA is aware that some firms have interpreted section 802(c) of the Act as allowing shipments of investigational drugs or devices to an *unlisted* country (a practice known as “transshipment”) as long as the shipment passes *through* a listed country. FDA disagrees with such an interpretation because the unrestricted transshipment of investigational drugs and devices from listed to unlisted countries would undermine the express limitation in section 802(c) of the Act.¹⁰ There is no indication that Congress intended to make listed countries act as mere transfer points for investigational drugs or devices that are destined for unlisted countries.

Exports under section 802(c) of the Act are subject to the recordkeeping requirement in section 802(g) of the Act. FDA regulations pertaining to such records can be found at 21 CFR 1.101(e). These exports, however, are not subject to the notification requirements of section 802(g) of the Act.

Additionally, as an alternative to section 802(c) of the Act in some circumstances, section 802(b)(1) of the Act authorizes exportation of an unapproved product, including an investigational

¹⁰ In contrast, exports to a listed country, followed by shipment to another listed country is permitted under section 802(c) of the Act, provided that the shipments are consistent with the laws of the importing countries, because that provision permits exportation of an investigational drug or device to any listed country.

new drug, to unlisted countries if the drug complies with the foreign country's laws and has valid marketing authorization in a listed country. Thus, exports under section 802(b)(1) of the Act may be made for investigational uses as well as for marketing purposes.

For exports of drugs for investigational use in unlisted countries where the drug product has not received valid marketing authorization in a listed country, the "312 program" requirements at § 312.110 remain applicable. On November 23, 2005, FDA issued a final rule to modify the regulations for the "312 program" (see 70 FR 70720). This final rule describes four mechanisms for exporting an investigational new drug product:

- First, the export may occur if the foreign clinical trial is covered by an IND. This means that the conduct of the foreign clinical trial will comply with FDA's IND requirements.
- Second, if the drug has marketing authorization in any country that is listed or described in section 802(b)(1)(A) of the Act, it may be exported to any country, including for investigational use. Neither an IND nor prior FDA approval is necessary. This mechanism corresponds to section 802(b)(1)(A) of the Act, and exports under this provision are subject to certain statutory requirements. For example, the export must not conflict with the foreign country's laws. Federal law also requires firms to notify FDA when they export products under section 802(b)(1) of the Act.
- Third, the export may occur if the drug is to be used in a clinical investigation in any country that is listed or described in section 802(b)(1)(A) of the Act. Neither an IND nor prior FDA approval is necessary. This mechanism corresponds to section 802(c) of the Act, and exports under this provision are subject to certain statutory requirements. However, federal law does not require firms to notify FDA when they export drugs under section 802(c) of the Act.
- Fourth, the export may occur, without prior FDA approval and without an IND, upon submission of a certification that the drug and export meet certain conditions as specified in the rule. This mechanism is the revised "312 program." In brief, the would-be exporter must certify to all of the following:

- The drug is intended for export;
- The drug is intended for investigational use in a foreign country;
- The drug meets the foreign purchaser's or consignee's specifications;
- The drug is not in conflict with the foreign country's laws;
- The outer shipping package is labeled to show that the drug is intended for export from the United States;
- The drug is not sold or offered for sale in the United States;
- The clinical investigation will be conducted in accordance with § 312.120;
- The drug is manufactured, processed, packaged, and held in substantial conformity with good manufacturing practices;
- The drug is not adulterated within the meaning of section 501(a)(1), (a)(2)(A), (a)(3), (c), or (d) of the Act;
- The drug does not present an imminent hazard to public health, either in the United States, if the drug were to be reimported, or in the foreign country; and
- The drug is labeled in accordance with the foreign country's laws.

The revised "312 program" also contains special provisions for exportation of an investigational new drug in the event of a national emergency in a foreign country where the national emergency necessitates exportation of an investigational new drug. The "national emergency" aspect of the "312 program" contemplates two different scenarios. In the first, the investigational new drug is to be stockpiled in the foreign country in anticipation of a national emergency so that the drug may be available for use if and when the national emergency arises. In the second, the investigational new drug is needed for use in a sudden and immediate national emergency in a foreign country. FDA developed the "national emergency" provisions for the "312 program" due to growing concerns about the possible use of biological, chemical, or other weapons in a terrorist attack and to the sudden emergence of new diseases. The "national emergency" provisions allow an exporter to export a drug under the "312 program" without making one or more of the certifications, but it also requires the Department of Health and Human Services to make certain decisions and, for

stockpile situations, requires FDA to approve exportation before exportation occurs.

Since enactment of the 1996 Amendments, most exports of investigational new drugs have occurred under section 802(c) of the Act or under the 312 program.

C. Impact of the 1996 Amendments on Devices Exported for Investigational Use

The 1996 Amendments also significantly affected investigational device exports. Section 802(c) of the Act permits a firm to export an unapproved device for investigational use in any of the listed countries, without prior FDA approval or an IDE. As in the case for drugs, the device must be exported in accordance with the laws of the foreign country, and the exports are subject to the recordkeeping requirement in section 802(g) of the Act as implemented by 21 CFR 1.101(e).

Yet, unlike the situation for drug exports, the 1996 Amendments permit device firms to export a device either under section 801(e)(2) of the Act or under section 802 of the Act. The authority selected is important because each section of the Act carries its own statutory requirements.

For example, if company F wants to export an unapproved device for investigational use to a listed country, it could:

- Export the device under section 801(e) of the Act. Under this provision, the exporter would need to comply with section 801(e)(1) of the Act and, depending on the device, might have to comply with section 801(e)(2) of the Act and submit information that would enable FDA to determine that exportation is not contrary to the public health and safety and that the foreign country approves of the exportation, *or*
- Export the device under section 802(b)(1)(A) of the Act if the device has received valid marketing authorization in any listed country. Section 802(b)(1)(A) of the Act permits exportation of an unapproved device, for any purpose, if the device complies with the laws of the foreign country and has received valid marketing authorization in a listed country. Exports under section 802(b)(1) of the Act may also occur to unlisted countries so long as the device complies with the foreign country's laws and has valid marketing authorization in a listed country. Exports

under this option must comply with the basic export requirements at section 802(f) of the Act (such as being in “substantial conformity” with cGMPs or meeting international standards as certified by a recognized international standards organization recognized by the Secretary and complying with section 801(e)(1) of the Act) and the notification and recordkeeping requirements in section 802(g) of the Act, *or*

- Export the device to a listed country under section 802(c) of the Act, without prior FDA approval or the submission of any information to FDA. However, under this option, compliance with the basic export requirements in section 802(f) of the Act and the recordkeeping requirement in section 802(g) of the Act and § 1.101(e) is necessary.

FDA’s regulation at 21 CFR § 812.18 reflects the options for exporting a device for investigational use, stating that a person exporting an investigational device subject to part 812 must obtain FDA’s prior approval under section 801(e)(2) of the Act *or* comply with section 802 of the Act.

A firm has the additional option of conducting the investigation under an IDE, in which case the IDE requirements in part 812 would apply to the export.

IX. Exports of Unapproved Drugs and Devices in Anticipation of Foreign Approval - Section 802(d) of the Act

Section 802(d) of the Act permits the exportation of an unapproved drug, biological product, or device “intended for formulation, filling, packaging, labeling, or further processing in anticipation of market authorization” in any of the listed countries. The only requirements for such exports are that:

- the use of the product must comply with the laws of the foreign country,
- the export must comply with the requirements in section 802(f) of the Act, and
- records for such exports must be kept in accordance with section 802(g) of the Act.

The range of activities covered under section 802(d) of the Act is very broad, although mere storage of an unapproved drug, biological product, or device would not constitute “formulation, filling, packaging, labeling, or further processing.” Additionally, FDA interprets the phrase “in anticipation of market authorization” as meaning that the firm exporting the product has filed an application or submission to obtain final marketing authorization in the foreign country. FDA does not consider an *intent* to seek market authorization or to file a marketing application at some future time to constitute “anticipation of market authorization.”

FDA also does not interpret section 802(d) of the Act as allowing *anyone* to export a drug as long as *someone* is seeking market authorization, irrespective of the laws of the foreign country at issue. Section 802(d) of the Act is commonly referred to as allowing firms to “fill the pipeline” so that a product will be available immediately upon market authorization by a foreign country. To interpret section 802(d) of the Act as allowing *any* firm to export the product so long as *someone* was seeking market authorization would essentially ignore the word “anticipation” of market authorization. Arguably, if a firm has not applied for market authorization, it cannot be “anticipating” market authorization. Thus, the word “anticipation” in section 802(d) of the Act suggests that the firm exporting the drug, biological product, or device is, in fact, the entity that is seeking market authorization or would be able to distribute that drug, biological product, or device legally upon marketing authorization.

Consequently, FDA interprets section 802(d) of the Act as follows. If the foreign country’s product approval process is specific to an application (i.e., to have marketing authorization, a firm

must submit an application, and the application must be approved), then a firm seeking to invoke section 802(d) of the Act to export a drug, biological product, or device to a foreign country must be seeking market authorization in that foreign country.

If, however, the foreign country's product approval process would allow multiple products on the market upon market authorization (i.e., once marketing authorization occurs, any person can market a drug, biological product, or device that meets the conditions of that marketing authorization), then a firm seeking to invoke section 802(d) of the Act to export a drug, biological product, or device to such a foreign country does not have to be the firm that sought marketing authorization in that foreign country.

This interpretation of section 802(d) of the Act acknowledges both the particular marketing authorization process in a foreign country and gives appropriate weight to the words "in anticipation of market authorization."

Please note that exports in anticipation of market authorization under section 802(d) of the Act are not subject to the simple notification requirement in section 802(g) of the Act. Instead, the exporter would send the simple notification to FDA once it receives market authorization and begins to export the product under section 802(b)(1)(A) of the Act.

X. Exports of Drugs and Devices for Diagnosing, Preventing, or Treating a Tropical Disease or a Disease “Not of Significant Prevalence in the United States” - Section 802(e) of the Act

The 1986 Amendments authorized exports of unapproved new drugs and biological products intended to prevent or to treat a tropical disease. Under the 1986 Amendments, the exporter had to submit an export application to FDA. The export application had to:

- Describe the drug being exported,
- list each country to which the drug would be exported,
- contain a certification that the drug would not be exported to a country if the agency could not find that the drug would be safe and effective in that country,
- identify the establishments where the drug is made, and
- show that other statutory requirements (such as compliance with cGMP's) are met.

FDA had to approve the export application before exportation could proceed.

The 1996 Amendments amended the tropical disease provision in several ways. The provision now covers drugs, including biological products, intended to *diagnose*, prevent, or treat tropical diseases; includes devices among the products eligible for exportation; and includes drugs, biological products, and devices that are intended to treat diseases that are “not of significant prevalence” in the United States. A disease that is “not of significant prevalence” in the United States can be one that is not manifested in many Americans (either because the pathogen is not common or because available treatments have made the disease rare in the United States) or is indigenous to a particular foreign country or to an area in another country. For example, measles may be considered to be a disease that is not of significant prevalence in the United States because most children are immunized against measles. As another example, poliomyelitis would be a disease that is not of significant prevalence in the United States because a Pan American Health Organization program eliminated polio in the Western Hemisphere in 1991.

However, like the 1986 Amendments, the 1996 Amendments require FDA to approve an export application before the product can be exported (see section 802(e) of the Act). The export

application should contain information showing that the drug or device is intended for use in the treatment of a tropical disease or a disease that is not of significant prevalence in the United States. Additionally, the application should contain information that will enable FDA to determine whether the drug, biological product, or device:

- Will not expose patients in the foreign country to an unreasonable risk of illness or injury, and
- will have a probable benefit to health that outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available drug or device treatment, provided that the product is used under conditions prescribed, recommended, or suggested in the labeling or proposed labeling. This includes information on the illness to be treated, the drug's risks, and the drug's benefits. By "currently available drug or device treatment," the applicant should consider the availability of products that are approved for the particular disease as well as those that are commonly used to treat the disease, even if the product is not approved for that indication.

FDA has not received any applications under section 802(e) of the Act. FDA will use a case-by-case approach on any application received under section 802(e) of the Act until it acquires sufficient expertise to state general criteria for these applications.

Persons interested in submitting an application under section 802(e) of the Act should contact the offices listed in part XII of this document.

XI. Export Notification and Recordkeeping

Under Section 802(g) of the Act

Section 802(g) of the Act requires persons exporting a drug or device under section 802(b)(1) of the Act to provide a “simple notification * * * identifying the drug or device when the exporter first begins to export such drug or device” to any country listed in section 802(b)(1) of the Act. If the product is to be exported to an unlisted country, section 802(g) of the Act requires the exporter to provide a simple notification “identifying the drug or device and the country to which such drug or device is being exported.”

With respect to all exports pursuant to section 802 of the Act, section 802(g) of the Act requires the exporter to maintain records of all drugs or devices exported and the countries to which they were exported.

A. *The Content of the Simple Notification*

FDA regulations, at 21 CFR 1.101(d), prescribe the content of the simple notification. The simple notification must contain:

- The product’s trade name,
- if the product is a drug or biological product, the product’s abbreviated or proper name or, if the product is a device, the type of device,
- if the product is a drug or biological product, a description of the product’s strength and dosage form or, if the product is a device, the product’s model number, and
- if the export is to a country not listed in section 802(b)(1) of the Act, the country that is to receive the exported article. The notification may, but is not required to, identify countries listed in section 802(b)(1) of the Act or state that the export is intended for a listed country without identifying the listed country. FDA acknowledges that section 802(g) of the Act and § 1.101(d) require exporters to identify the country that is to receive the exported product only if the country is not a listed country. However, FDA encourages exporters to identify listed countries that are to receive the exported product. Identification of the foreign country,

regardless of whether it is listed or not, will make it easier for FDA to meet its obligations under sections 802(a) and 802(f)(4), (f)(5), and (f)(6) of the Act which prohibit exports under certain conditions (such as a finding of an imminent hazard to the public health) and/or require FDA to consult with the “appropriate public health official” in the affected country.

If a firm declines to identify a listed country in its simple notification, FDA strongly recommends that the firm state that it exported the product to a listed country. This will inform FDA that the omission of a foreign country’s name was not an oversight. If it later becomes necessary for FDA to contact foreign health officials in a listed country, FDA will inspect the exporter’s records to determine where the exported products were sent. Inspections consume both time and resources for FDA and the affected firm, so FDA encourages voluntary disclosure of the listed countries receiving an exported product.

B. Where to Send the Simple Notification

Notifications should be sent to the following addresses:

For biological products and devices regulated by the Center for Biologics Evaluation and Research (CBER):

Division of Case Management (HFM-610),
Office of Compliance and Biologics Quality,
Center for Biologics Evaluation and Research,
Food and Drug Administration,
1401 Rockville Pike, Suite 200N,
Rockville, MD 20852-1448.

For human drug products and biological products regulated by the Center for Drug Evaluation and Research (CDER):

Division of New Drugs and Labeling Compliance (HFD-310),
Center for Drug Evaluation and Research,

Food and Drug Administration,
11919 Rockville Pike,
Rockville, MD 20852.

For devices:

Division of Program Operations (HFZ-305),
Center for Devices and Radiological Health,
Food and Drug Administration,
2094 Gaither Rd.,
Rockville, MD 20850.

C. Recordkeeping

As stated earlier, section 802(g) of the Act requires exporters to maintain records of all drugs and devices exported and the countries to which the products were exported. As provided by 21 CFR 1.101(e), this includes, but is not limited to, records showing:

- The product's trade name,
- if the product is a drug or biological product, the product's abbreviated or proper name or, if the product is a device, the type of device,
- if the product is a drug or biological product, a description of its strength and dosage form and the product's lot or control number or, if the product is a device, the product's model number,
- the consignee's name and address, and
- the date on which the product was exported and the quantity of product exported.

FDA regulations require that these records be kept at the site from which the products were exported or manufactured, and be maintained for the same period of time as required for records subject to good manufacturing practice or quality systems regulations applicable to the product. Under 21 CFR 1.101(e)(2), the records must be made available to FDA, upon request, during an

inspection for review and copying by FDA.¹¹

FDA regulations, at 21 CFR 1.101(b), also require records demonstrating compliance with section 801(e)(1) of the Act. The requirements for records demonstrating compliance with section 801(e)(1) of the Act are different from those required under section 802(g) of the Act. This guidance document discussed section 801(e)(1) of the Act and records in part V, above. Thus, because exports under section 802 of the Act must comply with the requirements in section 802(f) of the Act, and section 802(f) incorporates section 801(e)(1) of the Act, exports under section 802 of the Act must comply with the recordkeeping requirements of both 21 CFR 1.101(b) and 1.101(e).

Additionally, FDA reminds parties that they may need to maintain other records beyond those specified in section 802(g) of the Act. For example, firms whose products must be in substantial conformity with cGMP's under section 802(f)(1) of the Act may be subject to cGMP recordkeeping requirements under the regulations that apply to their products.

¹¹ On July 22, 2002, FDA stated, in response to a petition for reconsideration, that it would exercise enforcement discretion and not generally take enforcement action regarding § 1.101(b) insofar as it pertains to access to records held by food and cosmetic exporters while the agency considers whether any changes to that provision are necessary. On June 1, 2004, FDA published an advance notice of proposed rulemaking seeking comments on this issue (69 FR 30842).

XII. For Further Information Contact:

For animal drugs:

Division of Compliance (HFV-230),
Center for Veterinary Medicine,
Food and Drug Administration,
7519 Standish Place
Rockville, MD 20855,

240-276-9200

For biological products and devices regulated by CBER:

Division of Case Management (HFM-610),
Office of Compliance and Biologics Quality,
Center for Biologics Evaluation and Research,
Food and Drug Administration,
1401 Rockville Pike, Suite 200N,
Rockville, MD 20852-1448,

301-827-6201.

For devices:

Division of Program Operations (HFZ-305),
Center for Devices and Radiological Health,
Food and Drug Administration,
2094 Gaither Rd.,
Rockville, MD 20850,

240-276-0132

For drugs and biological products regulated by CDER:

Division of New Drugs and Labeling Compliance (HFD-310),
Center for Drug Evaluation and Research,
Food and Drug Administration,
5600 Fishers Lane,
Rockville, MD 20857,

301-827-8930.

For drugs exported for investigational use under § 312.110:

Office of International Programs (HFG-1),
Food and Drug Administration,

5600 Fishers Lane,
Rockville, MD 20857,

301-443-4480.

For foods and cosmetics:

Division of Enforcement (HFS-605),
Office of Compliance,
Center for Food Safety and Applied Nutrition,
Food and Drug Administration,
5100 Paint Branch Parkway,
College Park, MD 20740

301-436-2417

These offices listed above may have additional guidance documents and information on specific export topics or products.

For general policy questions:

Office of International Programs (HFG-1),
Food and Drug Administration,
5600 Fishers Lane,
Rockville, MD 20857,

301-827-4480 or 404-253-1221