program. For a complete description of each, see Addendum I (included in the application kit).

AR98–1 Human Subjects Requirements

AR98–2 Requirements for Inclusion of Women and Racial and Ethnic Minorities in Research

AR98–9 Paperwork Reduction Act Requirements

AR98–10 Smoke-Free Workplace Requirements

AR98–11 Healthy People 2000

AR98–12 Lobbying Restrictions

AR98–13 Prohibition on Use of CDC Funds for Certain Gun Control Activities

I. Authority and Catalog of Federal Domestic Assistance Number

This program announcement is authorized under Sections 391, 392, 393, and 394 [42 U.S.C. 280b, 280b–1, 280b–1a, and 280b–2] of the Public Service Act, as amended. The Catalog of Federal Domestic Assistance number is 93.136.

J. Where To Obtain Additional Information

The program announcement and application forms may be downloaded from the Internet: www.cdc.gov (look under funding). You may also receive a complete application kit by calling 1–888–GRANTS4. You will be asked to identify the program announcement number and provide your name and mailing address. A complete announcement kit will be mailed to you.

Please refer to Program Announcement 98070 when you request information.

If you have questions after reviewing the forms, for business management technical assistance, contact: Joanne Wojcik, Grants Management Specialist, Grants Management Branch, Procurement and Grants Office, Announcement 98070, Centers for Disease Control and Prevention (CDC), 255 East Paces Ferry Road, NE., Room 300, Mailstop E–13, Atlanta, GA 30305–2209, telephone (404) 842–6535, E-mail address jcw6@cdc.gov.

For program technical assistance, contact Wendy Watkins, Division of Violence Prevention, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (CDC), 4770 Buford Highway, NE., Mailstop K–60, Atlanta, GA 30341–3724, telephone (770) 488–4646, E-mail address dmw7@cdc.gov.

Dated: June 8, 1998.

John L. Williams,

Director, Procurement and Grants Office, Centers for Disease Control and Prevention (CDC).

[FR Doc. 98–15686 Filed 6–11–98; 8:45 am]

BILLING CODE 4163–18–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98D–0307]

Draft Guidance for Industry; Exports and Imports Under the FDA Export Reform and Enhancement Act of 1996

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance document entitled, ''FDA Draft Guidance for Industry on: Exports and Imports Under the FDA Export Reform and Enhancement Act of 1996.'' The draft guidance document addresses issues pertaining to the exportation of human drugs, animal drugs, biologics, food additives, and devices as well as the importation of components, parts, accessories, or other articles for incorporation or further processing into articles intended for export.

DATES: Written comments on the draft guidance document may be submitted by August 26, 1998. General comments on the agency's guidance documents may be submitted at any time.

ADDRESSES: Submit written comments on the draft guidance document to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Office of Policy (HF–23), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–3380.

SUPPLEMENTARY INFORMATION: FDA is announcing the availability of a draft guidance document entitled, ''FDA Draft Guidance for Industry on: Exports and Imports Under the FDA Export Reform and Enhancement Act of 1996.'' Enacted and later amended in 1996, the FDA Export Reform and Enhancement Act (Pub. L. 104–134, as amended by Pub. L. 104–180) significantly changed the export requirements for human drugs, animal drugs, biologics, devices, and, to a limited extent, food additives. For example, before the law was enacted, most exports of unapproved new drug products could only be made to 21 countries identified in section 802 of the Federal Food, Drug, and Cosmetic Act (the act), and these exports were subject to various restrictions. The FDA Export Reform and Enhancement Act amended section 802 of the act to allow, among other things, the export of unapproved new drugs to any country in the world if the drug complies with the laws of the importing country and has valid marketing authorization from any of the following countries: Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and the countries in the European Union (EU) and the European Economic Area (EEA). (Currently, the EU countries are Austria, Belgium, Denmark, Germany, Greece, Finland, France, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom. The EEA countries are the EU countries, Iceland, Liechtenstein, and Norway. The list of countries will expand automatically if any country accedes to the EU or becomes a member of the EEA.)

The draft guidance document provides information on the statutory requirements for exporting human drugs, animal drugs, biologics, and medical devices, general requirements for products exported under section 801 of the act (21 U.S.C. 381), labeling requirements for drugs and biologics exported under section 801(e) of the act, export requirements for unapproved drugs, biologics, and devices under section 802(b) of the act (21 U.S.C. 382(b)), exports of unapproved drugs and devices for investigational use, exports of unapproved drugs and devices in anticipation of foreign approval; exports of drugs and devices for diagnosing, preventing, or treating a tropical disease or a disease ''not of significant prevalence in the United States,'' export notifications to FDA, and ''import for export.''

The draft guidance document represents the agency's current thinking on exports and imports-for-export under sections 801 and 802 of the act. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the draft guidance document. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. A copy of the draft guidance document and received comments may be seen in the office

above between 9 a.m. and 4 p.m., Monday through Friday. The agency invites comments on the following issues:

• What are the draft guidance document's strengths and weaknesses? For example, which topics might require more explanation?

• Which international standards organization(s), if any, should FDA recognize for purposes of section 802(f)(1) of the act? Which international standards should be used and for which products? Under section 802(f)(1) of the act, all drugs and devices exported under section 802 of the act must be in substantial conformity with current good manufacturing practice requirements or meet ''international standards as certified by an international standards organization recognized'' by FDA.

• Section 802(e) of the act requires an application to export a drug or device intended to treat a tropical disease or a disease that is not of significant prevalence in the United States. FDA may approve exportation if it finds that the drug or device will not expose patients in the foreign country to an unreasonable risk of illness or injury and that the probable health benefits from using the drug or device under its labeled conditions of use outweigh the risk of injury or illness from its use, ''taking into account the probable risks and benefits of currently available drug or device treatment.'' What should the application contain so that FDA may make these findings? How many applications might be submitted?

The draft guidance document, with a table of contents and ''quick locator guide,'' can be accessed electronically at http://www.fda.gov/opacom/fedregister/frexport.html. The full text of the draft guidance document, without the table of contents and quick locator guide (due to reformatting and pagination changes in the **Federal Register**), follows:

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

I. Introduction

This guidance document is intended to summarize and to explain the basic requirements and procedures for exporting and importing human drugs, animal drugs, biologics, devices, food additives, color additives, and dietary supplements that may not be sold or distributed in the United States under the FDA Export Reform and Enhancement Act of 1996 (Pub. L. 104–134, and amended by Pub. L. 104–180).[1] 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, biologics, and devices.[2] In addition, the FDA Export Reform and Enhancement Act substantially reduced the requirements for exporting unapproved new animal drugs, provided a new option for exporting unapproved devices, and added a new provision, at section 801(d)(3) of the act that permits the import of certain components, parts, and accessories of human drugs, biologics, devices, food additives, color additives, and dietary supplements for further processing or incorporation into products intended for export.

This guidance document does not address export certificates and fees. Information on these subjects can be found in Compliance Policy Guide 7150.01, ''Certification for Exports.''

Please note that a firm or product may be subject to additional statutory or regulatory requirements beyond those described in this guidance. For example, depending on the type of products it manufactures, a firm may be subject to registration requirements under section 510 of the act (21 U.S.C. 360).

This guidance document represents the agency's current thinking with respect to the exportation of various products under the FDA Export Reform and Enhancement Act of 1996 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. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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 U.S. Code.

''cGMP'' means current good manufacturing practice. For drugs and biologics, cGMP regulations can be found at parts 210 and 211 (21 CFR parts 210 and 211). For devices, cGMP regulations 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 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 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 (Pub. L. 99–960). Most provisions in the 1986 Amendments were revised or eliminated by the 1996 Amendments.

''1996 Amendments'' means the FDA Export Reform and Enhancement Act of 1996 (Pub. L. 104–134 and amended by Pub. L. 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 regulation for PMA's can be found at 21 CFR part 814.

''312 Program'' means the regulatory program used by FDA for permitting the exportation of investigational drugs or biologics for clinical use in foreign countries. The principal statutory authority for the 312 Program is section 505(i) of the act, and the regulation can be found at § 312.110.

III. 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. Exports of Drugs and Biologics That May Not be Sold in the United States

The export provision in the act had its origins in 1906 as part of the Federal Food and Drugs Act (Pub. L. 59–384).

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

[2] If a product meets the requirements for sale in the United States, the act has no restrictions on its exportation.

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 remained essentially unchanged in the Federal Food, Drug, and Cosmetic Act of 1938 (Pub. L. 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, however, also defined the terms, ''drug,'' and ''new drug,'' and these definitions led to the conclusion that section 801(d)(1) of the act did not apply to new drugs. (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 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 (Pub. L. 99–960). Insofar as human drug products and biologics were concerned, the 1986 Amendments created section 802 of the act and established three separate ''tracks'' for exporting unapproved drugs and unlicensed biologics. Under ''track 1,'' FDA was authorized to approve an application for the export of new human and animal drugs and biologics 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 biologics 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 unapproved drugs and biologics to 21 countries. Although the 1986 Amendments provided criteria for adding more countries to the list, it did not provide any administrative mechanism for doing so. Consequently, exports 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 concept in the 1986 Amendments which required 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; 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); and 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. 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 (Pub. L. 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 countries and requiring the exporter to be pursuing product approval in the United States as a condition for allowing exportation). Consequently, an unapproved new

[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 seen in section 801(e)(1) of the act, and so exports could occur without prior FDA approval.

animal drug could be exported under section 802 of the act.

C. 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)) 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 (Pub. L. 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 began to generate criticism from the device industry. The device industry criticized the agency for the time FDA took to determine whether an export request met the statutory criteria. FDA reduced the average time for processing device export requests from an average of 91 days in 1992 to 10 days in 1995, yet, 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 (Pub. L. 104–134, and amended by Pub. L. 104–180) addressed industry's problems and concerns. For human drugs and biologics that may not be sold in the United States, the 1996 Amendments:

- Amended section 801(d) of the act to allow import of components of drugs and biologics into the United States that do not comply with other provisions in the act where those components are intended for incorporation or further processing by the initial owner or consignee into a drug or biologic that will be exported under section 801(e) or section 802 of the act or section 351(h) of the PHS Act.
- 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. 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 to be labeled in accordance with the act. If the drug's labeling includes conditions of 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 biologics intended for use in clinical investigations in any of 25 countries identified in section 802(b)(1)(A) of the act,
  - Authorized the export of 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 in anticipation of marketing authorization in a listed country, 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:

- Again restricted the authority to export an unapproved new animal drug to section 801 of the act.[4] However, unlike the situation that existed from 1968 to 1986, an unapproved new animal drug can be exported if it is: Intended for export; accords to the specifications of the foreign purchaser; is not in conflict with the laws of the importing country; is labeled on the outside of the shipping package that it is intended for export; and is not sold or offered for sale in interstate commerce (see section 801(e)(1) of the act).
- The only unapproved new animal drugs that cannot be exported under section 801 of the act are ''banned'' animal drugs (see section 801(e)(3) of the act). Neither the statute nor the legislative history explains what a ''banned'' animal drug is, and FDA is working on an interpretation as to what constitutes a ''banned'' animal drug.

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

- Amended section 801(d) of the act to permit the import of component parts, accessories, or other articles of a device that do not comply with other provisions in the act, if those component parts, accessories, or other articles are intended for incorporation or further processing by the initial owner or consignee into a device that will be exported under section 801(e) or section 802 of the act or section 351(h) of the PHS Act;
- Amended section 801 of the act to permit exportation of 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 25 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 in

[4] Animal drugs cannot be exported under section 802 of the act because that section pertains to biologics, devices, and *human* drugs.

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.''

Additionally, the 1996 Amendments permit importation of food additives, color additives, and dietary supplements into the United States if those articles are intended for incorporation or further processing by the initial owner or consignee into a drug, biologic, device, food, food additive, color additive, or dietary supplement that will be exported.

This document describes the requirements for drugs (both human and animal), biologics, and devices under sections 801 and 802 of the act and section 351(h) of the PHS Act, as amended by the 1996 Amendments. It begins with a discussion of the principal export requirements under sections 801 and 802 of the act and section 351(h) of the PHS Act, followed by a discussion of the ''import-for-export'' requirements under section 801 of the act.

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

Section 801(e)(1) of the act contains general requirements for any food, drug, device, or cosmetic that may not be sold in the United States and is intended for export. These requirements apply regardless of whether the product is exported under section 801(e) or section 802 of the act or section 351(h) of the PHS Act.[5] (Additional requirements apply to products exported under section 802 of the act and to devices exported under section 801(e)(2) of the act; those requirements are described later in this document).

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 product: 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.

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 with each element of section 801(e)(1) of the act.

To demonstrate that the product meets the foreign purchaser's specifications, FDA recommends that the firm exporting the product maintain records describing or listing the product specifications requested by the foreign purchaser. This would 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. 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.

To demonstrate that the product does not conflict with the laws of the importing country, FDA recommends that the firm obtain a letter from the foreign government agency, department, or other body stating that the product has marketing approval from the foreign government or does not conflict with that country's laws. Letters should *not* be from nongovernmental bodies or persons (such as company officials or attorneys in the foreign country). Additionally, if the letter from the foreign government is not in English, FDA recommends that the firm have an English-language translation of that document or be prepared to translate the document into English at the time of any FDA inspection. Such translations are essential because they will enable the firm to show, and for FDA to verify, that the product does not conflict with the laws of the importing country.

To demonstrate that the product is labeled on the outside of the shipping package that it is intended for export, FDA recommends that the firm place a statement on the shipping packages themselves. A statement such as ''For export only'' may be sufficient.

To demonstrate that the product is not sold or offered for sale in the United States, FDA recommends that the firm maintain records concerning the product, its labeling, and similar products sold or offered for sale in the United States. The labeling can simply state that the product is ''Not for sale in the United States,'' or bear a similar statement. As for the product itself, FDA examines whether the product (as opposed to batches, lots, or production runs of a product) is sold or offered for sale in the United States. For example, if company A makes five batches of a particular unapproved drug and intends to export two batches (and sell the remaining three batches in the United States), the fact that company A intends to export the two batches does *not* mean that the product is ''not sold or offered for sale in the United States.'' Instead, FDA considers the unapproved drug to be sold in the United States because other batches of the same product *are* sold in the United States.

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)), biologics, 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.

A. Special Requirements for Certain Devices

Some devices face 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 an unapproved 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 be deemed to be adulterated or misbranded unless, in addition to the requirements in section 801(e)(1) of the act, FDA has determined that exportation of the device is not contrary to the public health and safety and has the approval of the country to which it is intended for export.

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.

Although the act prohibits exportation of class III devices requiring premarket

[5] The requirements in section 801(e)(1) of the act apply to all products exported under section 802 of the act due to section 802(f)(3) of the act. That section 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 biologics exported under section 351(h) of the PHS Act.

approval unless the criteria under section 801(e)(2) of the act are met,[6] FDA, in exercising its enforcement discretion, has not taken enforcement action against those manufacturers who have not complied with the export criteria in section 801(e)(2) of the act, provided that the manufacturers have reasonably concluded that, if a report under section 510(k) of the act had been submitted to FDA, FDA would have granted 510(k) marketing clearance. FDA intends to continue exercising its enforcement discretion in this manner, with respect to the requirements in section 801(e)(2) of the act. FDA emphasizes, however, that it does not intend to exercise enforcement discretion with respect to the requirements in section 801(e)(1) of the act for manufacturers who reasonably believe that their devices would receive a 510(k) marketing clearance.

To help FDA determine whether exportation of the device is not contrary to the public health and safety, FDA recommends that manufacturers 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.[7] 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.[8]

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 manufacturer obtain a letter from the foreign country approving of the device's importation. If the manufacturer 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.'' (See ''For Further Information Contact'' in section XII of this document.)

B. Special Requirements for Partially Processed Biologics

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 (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 FDA requires such products to be licensed.[9]

Products that do qualify as partially processed biological products include intermediate biological products that a manufacturer has partially processed and that would be subject to licensure as final products after the completion of additional manufacturing steps. For example, synthetic peptides that are a component of an in vitro diagnostic test kit would be partially processed biological products.

FDA encourages persons who may be uncertain as to whether their products are partially processed biological products to contact the Import/Export Team in the Center for Biologics Evaluation and Research (see the ''For Further Information Contact'' in section 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 international manufacturing standards recognized by the agency. FDA will inspect manufacturers to ensure that they are in compliance with cGMP's.

FDA acknowledges that section 351(h) of the PHS Act also refers to ''international manufacturing standards as certified by an international standards organization'' recognized by FDA. At this time, FDA has not recognized any such international standards or organizations for purposes of section 351(h) of the PHS Act, but is examining this issue closely.

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 as 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

[6] Such devices may be eligible for export under section 802 of the act. (A discussion of section 802 of the act appears in section VI.B of this document.)

[7] 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 manufacturer provide a statement indicating whether an alternative test will be available to confirm the test results.

[8] A device may be considered to have an approved IDE if an institutional review board determines that the device is a nonsignificant risk device, and provided the device has met the requirements for nonsignificant risk devices under § 812.2(b).

[9] Unlicensed biologics that fail to qualify for export under section 351(h) of the PHS Act may qualify for export under section 802 of the act.

351(h) of the PHS Act, including the requirements section 801(e)(1) of the act. FDA recommends that the firm or manufacturer maintain the following records for possible review during a routine annual or biennial FDA inspection. Depending on the particular circumstances of export, different or additional records may also be relevant.

- Evidence that product for export qualifies as a partially processed biological product;
- Evidence that the partially processed biological product complies with the laws of the country to which it is being exported and accords to the specifications of the foreign purchaser, in accordance with section 801(e)(1) of the act, and is intended for further manufacture into final dosage form outside the United States, in accordance with section 351(h)(3) of the PHS Act. Such evidence may consist of a valid marketing authorization for the partially processed biological product or the final product from the foreign ministry of health, contractual agreement, and purchase orders that may include foreign specifications;
- Records, such as manufacturing records, that trace the partially processed biological product through the assignment of a batch or lot numbering system at the U.S. exporting firm. The agency suggests that these records also include temperature stability data for product during the conditions of transit (export) and periodic checks of the capacity of the shipping containers;
- Distribution records of exported partially processed biological products;
- Copies of all labeling that accompanies the partially processed biological product for export (i.e., container label or any package insert). FDA recommends that the partially processed biological product's container label state, ''Caution: For Further Manufacturing Use Only;'' and
- Evidence that the product is not intended for sale in the United States and has not been sold or offered for sale in the United States. This may consist of purchase orders from the foreign purchaser and distribution records and records of the product's labeling and similar products sold in the United States. FDA examines whether the product itself (as opposed to batches or lots) is sold or offered for sale in the United States. For example, if a company produces five batches of a partially processed biological product and intends to export two batches and sell the remaining three in the United States, the product is deemed ''sold or offered for sale in the United States'' and ''intended for sale in the United States'' within the meaning of section 351(h) of the PHS Act.

Additionally, firms that manufacture, prepare, or process partially processed biologics for export must register with FDA and list their products under section 510 of the act and parts 207 and 607 (21 CFR parts 207 and 607).

V. Labeling Requirements for Drugs and Biologics 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) [10] that may be sold in the United States. For these drugs, section 801(f) of the act imposes certain labeling requirements. If the drug that is approved in the United States is 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, section 801(f)(1) of the act specifies that the drug may be labeled in accordance with the foreign requirements and conditions for use *so long* as the drug is also labeled in accordance with the act.

For those 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 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 section 801(f) of the act is silent on this point, the agency suggests that the statement be in the foreign language because the requirement would be meaningless if foreign consumers could not read the statement and would have no value for U.S. consumers who, because section 801(e)(1)(D) of the act prohibits the exported product from being sold or offered for sale in domestic commerce, would not have access to the product when labeled for the unapproved use(s).

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 later in section 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. As discussed in section VII of this document, a drug exported under section 802 of the act is *not* subject to the labeling requirements in section 801(f) of the act.

VI. Exports of Unapproved Drugs, Biologics, and Devices Under Section 802(b) of the act

A. Drugs and Biologics

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

The 1996 Amendments, insofar as human drugs and biologics are concerned, modified the scope of section 802 of the act to state that the provision applies to drugs and biologics that: Require approval under section 505 of the act or, for biologics, 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 biologics and to approved human drugs and biologics being exported for unapproved uses. [11] If FDA declines to approve or license a drug or biologic or

[10] Insulin and antibiotics were excluded from section 801(f) of the act because they have historically 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 (Pub. L. 105–115) 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 requirements in section 801(e)(1) of the act.

[11] While section 802(b) of the act refers to drugs requiring approval under section 505 of the act, it does not apply to insulin, antibiotics, or over-the-counter drug products that do not require approval under section 505 of the act. In 1997, the Food and Drug Administration Modernization Act amended section 802 of the act so that exports of insulin and antibiotics are subject to the export requirements in section 801(e)(1) of the act.

decides to withdraw approval or revoke licensure for a drug or biologic and that product has been 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 intended for investigational use in a listed country, drugs intended for further processing or labeling to fill the pipeline in anticipation of marketing authorization in a listed country, and drugs intended to treat a tropical disease or disease that is ''not of significant prevalence in the United States.'' These provisions are discussed in greater detail in sections VII through IX 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.

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

Under section 802(f) of the act, the basic requirements for all drugs, biologics, and devices exported under section 802 of the act 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.[12] 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 GMP's 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)). The term does mean that the firm must 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)). FDA interprets the term ''substantial conformity'' under section 802(f)(1) of the act in a similar manner.
- 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 or made 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, or quality that it 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. As stated earlier, section 801(e)(1) of the Act requires that the drug or device to be exported: (1) Accords to the specifications of the foreign purchaser; (2) not conflict with the laws of the country to which it is intended for export; (3) be labeled on the outside of the shipping package that it is intended for export;[13] and (4) not be sold or offered for sale in domestic commerce.[14] (A discussion of the requirements in section 801(e)(1) of the act appears earlier in this guidance.)
- 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[15] which authorized it for marketing and the country to which it is being 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 is being exported. Additionally, a drug or device may not be exported if the drug or device is not promoted in accordance with these labeling requirements.

If the above requirements are not met, section 802(f) of the act states that a drug or device may not be exported. 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 primarily 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.

D. Exports of Unapproved New Drugs, Biologics, and Devices to a Listed Country—Section 802(b)(1)(A) of the Act

The principal provision authorizing the exportation of unapproved new drugs, biologics, 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.

[12] The agency has not recognized an international standards organization or standard for any FDA-regulated product for purposes of section 802(f) of the act, but is examining this issue closely.

[13] A statement on the outside of the shipping package, such as, ''For export only'' or similar language, may be sufficient.

[14] As stated in section IV of this document, FDA advises firms to maintain records concerning the product, its labeling, and similar products sold in the United States. The product's labeling can state that the product is ''Not for sale in the U.S.'' or use similar language.

[15] The listed countries, under section 802(b) of the act, are: Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and the member nations of the European Union and the European Economic Area. As of January 1, 1998, the EU countries are Austria, Belgium, Denmark, Germany, Greece, Finland, France, Ireland, Italy, Luxembourg, the Netherlands, Portugal, 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 as long as the drug or device meets applicable requirements of the act, without submitting an export request to FDA or receiving FDA approval to export the drug or device. Moreover, in a change from the 1986 Amendments, firms do *not* have to seek U.S. approval of the product as a condition of exportation.

FDA interprets the terms ''marketing authorization'' as meaning an affirmative decision by the appropriate public health authority in a foreign country to permit the drug, biologic, or device to be sold in that country. For example, if country D approves a drug for investigational use, the approval would not constitute ''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 ''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 would consider a drug, biologic, or device to have ''marketing authorization'' if the listed country does not object to the product's marketing, and 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, 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 must 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. [16]

A similar concept applies 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.

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 is not closed. The 1996 Amendments contain 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 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 cGMP's, (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.

The authority to add countries to the list, by law, cannot be delegated below the Office of the Secretary. Thus, FDA has no authority to add countries to the list.

F. Exports of Unapproved New Drugs and Biologics 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 biologics) to a foreign country, but none of the listed countries has approved the drug for marketing, it has two other options for exporting the product. [17]

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 authorization by the ''responsible authority'' in that country, and
- The agency 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 authorizes 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 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 the listed 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.

The second option is in section 802(b)(3) of the act. This section permits a firm to petition the agency to approve 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 must allow exportation of the drug if:

- The person exporting the drug: (1) Certifies that the drug would not meet

[16] Additionally, under the 1986 Amendments, FDA approved exports of drugs that varied, in limited respects, from drugs that were the subject of an IND or a marketing application. The 1986 Amendments required firms to be actively pursuing market approval of the drug in the United States as a condition for exportation; this condition no longer exists in the act.

[17] The requirements in sections 802(b)(2) and (b)(3) of the act do *not* apply to devices. Congress omitted devices from these provisions to the act 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 provide an acceptable alternative.

the conditions for approval under the act or the conditions for approval in a listed country; and (2) provides ''credible scientific evidence'' 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 biologics), 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. A letter from the relevant foreign government entity addressing each item in this paragraph should be acceptable.

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.

Persons who wish to export a drug under sections 802(b)(2) or 802(b)(3) of the act should send their documentation or requests to:

(For Biologics), Division of Case Management (HFM–610), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, rm. 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.

FDA has 60 days to act on a request to export a drug under section 802(b)(3) of the act. The agency will begin the 60 day period on the date that it *receives* a *complete* petition containing the certification and evidence required by the act.

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

A. 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 section 801 of the act was interpreted as not applying to ''new drugs.'' Instead, FDA regulated the exportation of unapproved new drugs (including biologics) 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 since then. These regulations were codified at § 312.110 (the part of the *Code of Federal Regulations* pertaining to investigational drugs), 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.

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 Drug Exports for Investigational Use

The 1996 Amendments changed 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 FDA interprets section 802(c) of the act as applying only to investigational drugs and devices exported to the *listed* countries. The agency is aware that some firms have interpreted this provision as permitting transshipment to *unlisted* countries, but section 802(c) of the act is silent with respect to transshipment, and a more reasonable interpretation would be that transshipments are *not* allowed under section 802(c) of the act. Interpreting section 802(c) of the act to allow transshipment would presume that the listed countries may serve as mere transfer points or conduits for investigational drugs and devices destined for unlisted countries (when neither the statute nor its legislative history support such a presumption) and would make the limitation to the listed countries in section 802(c) of the act virtually meaningless.

Additionally, one should note that section 802(b)(1) of the act authorizes exportation to unlisted countries if the drug complies with the foreign country's laws and has valid marketing authorization in a listed country. Exports under section 802(b)(1) of the act may be made for investigational uses or 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. However, FDA is considering possible revisions to the regulations for the ''312 program'' due to sections 802(b) and (c) of the act as well as additional changes to the program.

C. Impact of the 1996 Amendments on Device Exports for Investigational Use

The 1996 Amendments also affected device exports significantly. 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. However, as in the case for drugs, the device must be exported in accordance with the laws of the foreign country.

Yet, unlike the situation for drug exports, the 1996 Amendments give device manufacturers the option whether to export a device under section 801(e)(2) of the act or under

section 802 of the act. The selected authority 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)(2) 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 submit information that would enable FDA to determine that exportation is not contrary to the public health or 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 cGMP's or meeting international standards as certified by a recognized international standards organization 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 is necessary.

Consequently in the **Federal Register** of May 13, 1997 (62 FR 26228), FDA amended § 812.18 to state 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.

Of course, a firm always has the additional option of conducting the investigation under an IDE, in which case the IDE requirements in part 812 would apply.

VIII. 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, biologic, or device ''intended for formulation, filling, packaging, labeling, or further processing in anticipation of market authorization'' in any of the listed countries. The only express requirements for such exports are that the product comply with the laws of the foreign country and the requirements in section 802(f) of the act. 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, biologic, 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 manufacturer 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 advises firms that export a product in anticipation of market authorization, under section 802(d) of the act, to notify FDA when they export the product. The notification should identify the drug, biologic, or device being exported and the country receiving the product. Notification when a product is exported under section 802(d) of the act is consistent with section 802(f) of the act. As stated earlier, section 802(f) of the act establishes conditions for all products exported under section 802 of the act. For example, a product cannot be exported under section 802 of the act if it is not in substantial conformity with cGMP's. Yet, if firms do not notify FDA about the products that have been exported, FDA cannot determine whether products exported under section 802(d) of the act comply with cGMP's.

Additionally, notification is consistent with a practical interpretation of section 802(g) of the act which requires exporters of drugs, biologics, and devices to provide a simple notification to the agency when they export a product to a listed country or to an unlisted country under section 802(b)(1) of the act. Section 802(b)(1) of the act permits exports when the drug, biologic, or device has received market authorization in a listed country, whereas section 802(d) of the act permits exports to a listed country in anticipation of market authorization. A literal interpretation of section 802(g) of the act would not require an exporter to notify FDA when it shipped a product to a listed country in anticipation of market authorization, but would instead require the exporter to notify FDA when the exporter shipped the same product to the same country once it received market authorization. It would be more practical, simple, and efficient–both for exporters and FDA– if exporters notify FDA when they export a product in anticipation of market authorization, under section 802(d) of the act, rather than wait for market authorization in the listed country and then notify FDA.

Details on notification under section 802(g) of the act appear later in this guidance.

IX. 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 biologics 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: (1) Describe the drug being exported, (2) list each country to which the drug would be exported, (3) 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, (4) identify the establishments where the drug is made, and (5) 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 intended to *diagnose*, prevent, or treat tropical diseases, includes devices among the products eligible for exportation, and includes drugs, biologics, 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.

However, like the 1986 Amendments, the revised provision (which is now codified as section 802(e) of the act) requires FDA to approve an export application before the product can be exported. The export application should contain information showing that the drug or device is intended for use in 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, biologic, or device:

- Will not expose patients in the foreign country to an unreasonable risk of illness or injury, and
- When used under conditions prescribed, recommended, or suggested in the labeling or proposed labeling has 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. 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.

X. Export Notification 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.''

In all cases, 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 suggests that, to identify a drug or device, the exporter describe in the notification the product's name or type of device, its generic name, and a description of its strength and dosage form (if the product is a drug) or the product's model number (if the product is a device).

As for identifying the country that is to receive the exported product, FDA acknowledges that section 802(g) of the act requires 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 the country that is to receive the exported product in all cases, regardless of whether the country is among those listed in section 802(b)(1) of the act. Identification of the foreign country, regardless of whether it is listed or not, helps FDA 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 requires FDA to consult with the ''appropriate public health official'' in the affected country.

B. Where to Send the Simple Notification

Notifications may be sent to the following addresses:

For biological drug products and biological devices: Division of Case Management (HFM–610), Office of Compliance, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, rm. 200N, Rockville, MD 20852–1448.

For human drug products: Division of Labeling and Nonprescription Drug Compliance (HFD–310), Center for Drug Evaluation and Research, Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855–2737.

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. FDA recommends that exporters maintain records showing:

- The product's name and its generic name (if the product is a drug or a device),
- The type of device (if the product is a device),
- A description of its strength and dosage form and the product's lot or control number (if the product is a drug) or the product's model number (if the product is a device),
- The consignee's name and address, and
- The date and quantity of product exported.

FDA recommends that these records be kept at the site from which the products were exported and be maintained at least 5 years after the date of exportation. The agency may request that the records be made readily available for review and during an agency inspection.

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.

XI. ''Import for Export''—Section 801(d)(3) and (d)(4) of the Act

Before the 1996 Amendments, all imported components of drugs, biologics, devices, and other FDA-regulated products had to comply with the requirements of the act, even if they were to be incorporated into products destined solely for export.

The 1996 Amendments changed the law by creating two subsections at 801(d)(3) and (d)(4) of the act. Under section 801(d)(3) of the act, a component of a drug or a biologic, a component part, accessory, or other article of a device, or a food additive, color additive, or dietary supplement that would otherwise be refused entry into the United States, can be imported into the United States if:

- The importer submits a statement to the agency at the time of initial importation declaring that the component, part, accessory, or article is intended to be ''incorporated'' or ''further processed'' by the initial owner or consignee into a drug, biological product, device, food, food additive, color additive, or dietary supplement that will be exported from the United States by the initial owner or consignee in accordance with section 801(e) or section 802 of the act or section 351(h) of the PHS Act (see section 801(d)(3)(A) of the act).
- The initial owner or consignee responsible for the imported article maintains records that identify the use of the imported component, part, accessory, or article. Upon request from the agency, the initial owner or consignee must submit a report that accounts for the exportation or the disposition of the imported component, part, accessory, or article (including quantities that were destroyed), including the manner in which the initial owner or consignee complied

with the requirements in section 801(d) of the act (see section 801(d)(3)(B) of the act).

• Any imported component, part, accessory, or article that is not incorporated into a product must be destroyed or exported by the owner or consignee (see section 801(d)(3)(C) of the act).

This provision is commonly referred to as the ''import for export'' provision.

A. Items Covered Under the Import for Export Provision

1. *Human Drugs*

One issue under section 801(d)(3) of the act is what constitutes a ''component'' of a drug. FDA regulations define ''component'' as meaning ''any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.'' (See § 210.3(b)(3).) Additionally, for purposes of section 801(d) of the act, FDA interprets the term ''component'' broadly to include a range of items, such as the active and inactive ingredients for a drug or biologic, bulk drugs, and even unapproved foreign versions of drugs that are approved for use in the United States. So, for example, if company X wants to import a bulk drug from a source that differs from the bulk drug source it uses for products sold in the United States, company X may import the bulk drug from the different source provided that company X incorporates the bulk drug into a product for export or further processes the bulk drug before exporting it (or otherwise destroys the bulk drug). The imported bulk drug from the different source *cannot* be used in the product to be sold in the United States.

Additionally, an item can be a ''component'' if it is intended for ''further processing'' in the United States before being exported to another country. For example, a finished dosage form that is sterilized in the United States would be a ''component'' within section 801(d)(3) of the act (because the drug is ''further processed'' during the sterilization process).

2. *Devices*

For devices, FDA regulations define a ''component'' as ''any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.'' (See § 820.3(c).) As in the case of drugs and biologics, FDA interprets the term ''component'' in section 801(d) of the act broadly to encompass a range of items.

Yet, regardless of whether the imported item is a drug or device component, the key issue under section 801(d)(3) of the act is how the component will be ''incorporated'' or ''further processed.''

3. *Food Additives, Color Additives, and Dietary Supplements*

Section 801(d)(3) of the act refers to food additives, color additives, and dietary supplements. The act defines ''food additive'' at section 201(s) of the act, ''color additive'' at section 201(t) of the act, and ''dietary supplement'' at section 201(ff) of the act.

B. Activities Covered Under the Concept of ''Incorporation'' and ''Further Processing''

Section 801(d)(3) of the act only permits a component, part, accessory, or article to enter the United States if it is intended to be ''incorporated'' into a product for export or is to be ''further processed'' into a product that will be exported.

In the context of section 801(d)(3) of the act, FDA interprets the terms ''incorporated'' and ''further processing'' to encompass a wide range of activities. Thus, ''incorporation'' and ''further processing'' are not confined to product manufacture. Instead, they include related activities such as packaging and labeling of finished products and specialized processing (such as sterilization) of a product.

However, FDA does *not* consider a component, part, accessory, or article to be ''incorporated'' or ''further processed'' if it is merely stored in the United States before being exported elsewhere. Although FDA has exercised enforcement discretion regarding specific entries of violative products that are stored in the United States, the agency does not consider the importation of an unapproved product for storage purposes to fall within the meaning of ''incorporated'' or ''further processed'' under section 801(d)(3) of the act.

C. Submission of Statements to FDA

Section 801(d)(3)(A) of the act requires the importer to submit, ''at the time of initial importation,'' a statement to the agency indicating that the imported component, part, accessory, or other article is intended to be incorporated or further processed by the initial owner or consignee into a product that will be exported in compliance with section 801(e) or section 802 of the act or section 351(h) of the PHS Act. Firms should submit this statement to FDA *each time* they import an article under the ''import for export'' provision in the act. The statement (along with other import documents) should be provided to the FDA field office that has responsibility over the port or site of entry into the United States.

FDA recommends that the statement contain the following information:

• The purpose for which the article is being imported prior to export (how it will be further processed or the name or description of the product into which it will be incorporated);

• The imported article's name or description (including any scientific or technical name);

• Any product coding, batch, lot, or other identifying numbers;

• The name and address of the imported article's foreign manufacturer (if different from the name of the foreign shipper identified in the import records at the U.S. Customs Service); and

• The name and address of the initial owner or consignee in the United States and, if different, the address in the United States where the imported article will be further processed or incorporated into a product for export.

For blood, blood components, source plasma, source leukocytes, or a component, accessory, or part that is not licensed under section 351(a) of the PHS Act and is to be imported under section 801(d)(4) of the act, FDA suggests that the statement include a copy of the determination by FDA granting permission to import the product or article. (The request for determination is described in more detail later in section XI.E.3 of this document.)

FDA emphasizes that, under section 801(d) of the act, the imported article *must* ultimately be further processed or incorporated into a product that is exported in accordance with the act's export provisions from the United States or the imported article must be destroyed. The imported article *cannot* be used in any product which is to be introduced into U.S. commerce.

The agency intends to issue regulations covering statements under section 801(d) of the act.

D. Records to be Retained and Reports to be Submitted for Exports Under Section 801(d)(3) of the Act

Section 801(d)(3)(B) of the act requires the initial owner or consignee responsible for an imported article to ''maintain records that identify the use of such imported article and upon request * * * [to] submit[ ] a report that provides an accounting of the exportation or disposition of the imported article, including portions that have been destroyed, and the manner in

which such person complied with the requirements of this paragraph * * *.''

The statutory reference to the *initial* owner or consignee indicates that, under section 801(d)(3) of the act, the person who imports the article for incorporation or further processing may, in turn, have other persons perform the actions that lead to the incorporation or further processing of the imported article. For example, if company C imports a drug into the United States for sterilization purposes, but does not have the technological capability to sterilize the drug itself, company C could send the drug to company D for sterilization and, after receiving the sterilized drug back from company D, export the drug from the United States. However, under this scenario, company C would remain the owner of the product and would be responsible for maintaining records and for submitting, upon FDA's request, a report accounting for the exportation or disposition of the imported article.

The agency suggests that firms importing an article into the United States under section 801(d)(3) of the act retain records showing:

- The name or description of the article (including any scientific or technical name);
- Any product coding, lot, batch, or other identifying numbers;
- The name and address of the foreign manufacturer of the imported article;
- How the article will be or was further processed, and the name and description of any product into which it will be or was incorporated in the United States;
- The signature of the responsible person at the importing firm;
- The name and address of the firm in the United States where the article will be or was further processed or incorporated into another product;
- The disposition of the imported article, i.e., manufacturing records showing how specific articles were used or destroyed and the dates of receipt, use, destruction, and/or reexportation, as that information becomes available;
- Any product coding, lot, batch, or other identification number for the further-processed article or product incorporating the imported article;
- A copy of the label to be applied to the shipping package, container, or crate used to export the further-processed article or product incorporating the imported article (indicating that it contains articles that may not be sold or offered for sale in the United States and are intended for export only); and
- The name and address of the foreign purchaser of the further-processed article or product incorporating the imported article.
- Additionally, for blood, blood components, source plasma, source leukocytes, or a component, accessory, or part thereof (including blood or plasma derivatives or intermediates) that is not licensed under section 351(a) of the PHS Act and is to be imported under section 801(d)(4) of the act, the agency recommends that the records also include documentation of the agreement between the foreign material supplier and the U.S. manufacturer. The documentation should outline the specific contractual relationship, the foreign manufacturing specifications, and the U.S. manufacturer's plan for auditing the foreign supplier to ensure compliance with the terms of the contract. FDA suggests that the initial owner or consignee have written standard operating procedures to ensure that such products are not diverted to domestic use in the United States and are kept segregated from and not co-mingled with products or components intended for use in the United States (e.g., quarantine procedures used for segregating imported blood, blood components, or final products from products intended for use in the United States, including validation data for procedures to clean equipment and facilities used for manufacturing products for use in the United States and exported products).

FDA also encourages firms to maintain any other records that would assist FDA in determining whether they comply with section 801(d)(3) or (d)(4) of the act.[18] FDA suggests that firms retain records relating to the importation of an article for incorporation or further processing in the United States for 5 years after the destruction or exportation of the last imported component, part, accessory, or article for a particular lot or batch. The records may be maintained at the importing firm's site and may be subject to inspection by FDA.

FDA intends to issue regulations to establish recordkeeping requirements, and persons subject to this provision should note that the act specifically prohibits the making of a knowingly false statement in any record or report required under section 801(d)(3)(A) or (d)(3)(B) of the act as well as the failure to submit or maintain records under these sections of the act (see section 301(w) of the act).

E. Special Requirements for Blood, Blood Components, Plasma, Source Leukocytes, and Tissues—Section 801(d)(4) of the Act

1. Blood, Blood Components, Plasma, and Source Leukocytes

The ''import for export'' requirements for blood,[19] blood components,[20] plasma,[21] and source leukocytes[22] differ from those for drugs and other biologics. Under section 801(d)(4) of the act, the importation of these products, components, accessories, or parts is not permitted under section 801(d)(3) of the act *unless* the importation complies with section 351(a) of the PHS Act *or* the agency permits the importation ''under appropriate circumstances and conditions.'' (FDA intends to issue regulations specifying the ''appropriate circumstances and conditions'' that would allow importation of unlicensed products under the import for export authority.)

Under section 801(d)(4) of the act, FDA may permit the import for export of blood and blood components, source plasma, source leukocytes, or a component, accessory, or part thereof, which may not be licensed or meet cGMP requirements. Products imported under section 801(d)(4) of the act must also comply with section 801(d)(3) of the act.[23]

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[18] A firm may also be subject to certain recordkeeping requirements outside those described in section 802(g) of the act. For example, because all drugs and devices exported under section 802 of the act must be in substantial conformity with cGMP's or international standards recognized by FDA, there may be cGMP recordkeeping requirements that apply to the exported drug or device.

[19] FDA interprets ''blood'' as whole blood collected from a single donor and processed either for transfusion or further manufacturing (see § 606.3(a) and the regulation for whole blood at 21 CFR 640.1).

[20] Under FDA regulations, a ''blood component'' is that part of a single-donor unit of blood separated by physical or mechanical means (see § 606.3(c) and part 640 (21 CFR part 640)).

[21] Under § 640.60, ''source plasma'' is the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use. The term does not extend to single donor plasma products intended for intravenous use.

[22] FDA interprets ''source leukocytes'' as leukocytes collected for further manufacturing by leukapheresis (as defined in § 606.3(g)). This is a procedure in which blood is removed from the donor, the leukocyte concentrate is separated, and the remaining formed elements and residual plasma are returned to the donor.

[23] A U.S. manufacturer that intends to incorporate or further process certain imported blood products for export, or the foreign supplier of such material, may submit an import for export request under section 801(d)(4) of the act. Section 801(d)(3) of the act specifies that the *importer* must submit the statement of intent to export to the Secretary, and that the *initial owner or consignee responsible for* the imported article must maintain certain records and submit a report upon request. A U.S. firm that intends to perform processing or manufacturing steps involving an imported blood product under section 801(d)(4) and (d)(3) of the act should have sufficient information, to submit to FDA in support of an import for export request, that allows FDA to

Licensed blood products, such as licensed source plasma, may be imported if such importation complies with section 351(a) of the PHS Act. Other licensed blood products, such as those having cGMP deficiencies, are not considered to be in compliance with section 351(a) of the PHS Act. If a product does not have a license or is considered to be in noncompliance with section 351(a) of the PHS Act, the manufacturer that wishes to import such a blood product for incorporation or further processing into a product for export may seek FDA's permission to import the product. CBER will evaluate such import for export requests on a case-by-case basis.

Recovered plasma and serum are blood products currently not subject to licensure. Recovered plasma and serum that are intended for further manufacture or incorporation into products for export must be imported in accordance with the short supply provisions at 21 CFR 601.22. Recovered plasma and serum intended for further manufacturing or incorporation into noninjectable products not subject to licensure may be imported without an import for export submission if they are manufactured in accordance with cGMP's and are labeled appropriately. Labeling for such products should include the applicable container label requirements listed in § 606.121. A firm may apply to import recovered plasma and serum that do not meet cGMP's by submitting an import for export request. CBER will evaluate these requests on a case-by-case basis.

Thus, under section 801(d)(4) of the act, no person may import blood products that are: (1) Subject to licensure and do not comply with section 351(a) of the PHS Act; or (2) are not subject to licensure and do not comply with cGMP's, without FDA's prior permission. For the latter, failure to seek and obtain FDA's permission, under section 801(d)(4) of the act, prior to importation may be a criminal violation.

FDA further recommends that persons who intend to import blood products under section 801(d)(4) of the act register and list or update their registration and listing to include a description of the imported material and the final product for export that will be manufactured from or incorporate the imported biological material. Registration and listing information should not be contained in the import for export request, but may instead be sent to the appropriate registration office listed in parts 207 or 607. Additionally, the agency requests that U.S.-licensed facilities receiving any foreign biological components or products, other than blood, under section 801(d)(3) of the act which will be used for manufacture into a product for export report such changes in accordance with 21 CFR 601.12.

2. Tissues

For tissues and tissue parts or components, section 801(d)(4) of the act prohibits importation unless the importation complies with section 361 of the PHS Act. (Section 361 of the PHS Act authorizes the issuance of regulations to control communicable diseases.) Thus, tissues and their parts or components must comply with the PHS Act and regulations issued under the PHS Act in order to enter the United States, even if the product is ultimately destined for exportation.

Persons who intend to import tissues and tissue parts or components (intended for transplantation) under section 801(d)(4) of the act should comply with the regulations at part 1270 (21 CFR part 1270) and also comply with the notification requirement in section 801(d)(3)(A) of the act. Under § 1270.42, the importer of record must notify the director (or his or her designee) of the FDA district having jurisdiction over the port of entry, and the tissue must be held until FDA releases it. If the human tissue that is imported for further processing or incorporation into a product for export is kept in quarantine at all times, it does not have to meet all the screening and testing requirements in part 1270. If the tissue is declared and identified as being in quarantine, it must be accompanied by records assuring identification of the donor and indicating that the tissue has not been determined to be suitable for transplantation (see § 1270.33(c)). The owner or consignee in the United States must prepare and follow written procedures for designating and identifying quarantined human tissue and preventing infectious disease contamination or cross-contamination during processing (as stated in § 1270.31).

If an importer, consignee, or U.S. manufacturer delivers or ships human tissue or a component thereof before FDA releases it or fails to quarantine tissue that has not been determined to be suitable for human transplantation, such action may constitute a criminal violation.

3. Requests to Import Blood, Blood Components, Plasma, and Source Leukocytes for Further Processing or Incorporation into a Product for Export (''Requests for Determination'')

Section 801(d)(4) of the act does not specify how persons who wish to import blood, blood components, source plasma, source leukocytes, or their components, accessories, or parts obtain permission to import those products. Nevertheless, to facilitate imports under section 801(d)(4) of the act, FDA recommends that manufacturers provide an import for export request which demonstrates that appropriate circumstances or conditions warrant CBER's approval of importation under section 801(d)(4) of the act. The agency recommends that these requests, known as a ''request for determination,'' contain the following information:

- The names and addresses of the foreign manufacturer of the article to be imported and the initial owner or consignee in the United States that would be responsible for the further processing or incorporation of the article into another product;
- The specific identity of the article to be imported and details as to how the imported article will be further processed or incorporated into a product for export;
- A description of the standard operating procedures and safeguards that the initial owner or consignee in the United States will use or implement to ensure that the imported articles or products incorporating such articles are segregated from and not comingled with products, components, accessories, or parts intended for use in the United States (e.g., quarantine procedures used for segregating imported blood, blood components, or final products from products intended for use in the United States, including validation data for procedures to clean equipment and facilities used in manufacturing products for use in the United States and products for export);
- General donor screening questionnaire or criteria, translated into English, that will be used to screen donors;
- A certification that the foreign supplier will perform tests for infectious disease on the blood, blood components, source plasma, or source leukocytes, or their components, accessories, or parts (including blood or plasma derivatives or intermediates) at the time of donation and before importation to the United States, and the expected results of such tests. The infectious disease agents that should be tested for include, but are not limited to:

make the determination whether appropriate circumstances and conditions exist to permit such importation.

HIV–1, HIV–2, hepatitis B virus, hepatitis C virus, HTLV-I, HTLV-II, and Treponema palladum. A request for determination may be based upon infectious agent tests performed using test kits other than those licensed or approved by FDA. In such cases, FDA suggests that the request contain a copy of the labeling for the test kit used, translated into English, as part of the submission; and

• A copy of the product's label. FDA recommends that the label include information such as the product's descriptive name; the name(s) and address(es) of establishments collecting, preparing, labeling, or pooling the source material; donor, lot, or pool numbers relating the unit to the donor; the recommended storage temperature (in degrees Celsius); the product's quantity; statements such as ''Import for Export,'' ''Not for Use in Products Subject to Licensure Under Section 351 of the Public Health Service Act,'' and ''For Manufacturing Use Only'' or ''For Manufacturing into Noninjectable Products Only;'' statements indicating that the product has been tested for infectious disease agents and, if the product has tested positive for an infectious disease agent, the term ''BIOHAZARD'' as well as any other appropriate warnings or special handling instructions.

A request for determination may be sent to the Center for Biologics Evaluation and Research, Office of Compliance, Division of Case Management (HFM–610), 1401 Rockville Pike, Rockville, MD 20852–1448. If FDA determines that the blood, blood component, source plasma, or source leukocyte, or a component, accessory, or part meets the appropriate circumstances and conditions to permit its importation into the United States, FDA will notify the person requesting the determination that it has granted permission to import the article.

XII. For Further Information Contact:

For animal drugs: Drugs Team, Division of Compliance, Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1785.

For biologics: Division of Case Management (HFM–610), Office of Compliance, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, rm. 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, 301–594–4699.

For drugs: Division of Labeling and Nonprescription Drug Compliance (HFD–310), Center for Drug Evaluation and Research, Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855–2737, 301–594–0063.

For drugs exported for investigational use under § 312.110: Office of International Affairs (HFG–1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4480.

For food additives, color additives, and dietary supplements: Office of Field Programs (HFS–602), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–205–4187.

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

For general policy questions: Office of Policy (HF–23), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–3344.

Dated: June 2, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration.

[Document Identifier: HCFA–724]

Agency Information Collection Activities: Submission for OMB Review; Comment Request

AGENCY: Health Care Financing Administration.

In compliance with the requirement of section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, the Health Care Financing Administration (HCFA), Department of Health and Human Services, is publishing the following summary of proposed collections for public comment. Interested persons are invited to send comments regarding this burden estimate or any other aspect of this collection of information, including any of the following subjects: (1) The necessity and utility of the proposed information collection for the proper performance of the agency's functions; (2) the accuracy of the estimated burden; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) the use of automated collection techniques or other forms of information technology to minimize the information collection burden.

Type of Information Collection Request: Extension of a currently approved collection; *Title of Information Collection:* Medicare/Medicaid Psychiatric Hospital Survey Data and Supporting Regulations Contained in 42 CFR 482.60, 482.61 and 482.62; *Form No.:* HCFA–724 (OMB# 0938–0378); *Use:* The information collected on this form will assist HCFA in maintaining an accurate data base on providers participating in the Medicare psychiatric hospital program. The HCFA–724 has two parts; part one is completed by the facility (i.e., location, number of beds, number of admissions) and part two is completed by the survey team (i.e, dates of survey, type of survey, survey team composition); *Frequency:* Annually; *Affected Public:* Federal government, Business or other for-profit, Not-for-profit institutions, and State, local or tribal government; *Number of Respondents:* 350; *Total Annual Responses:* 350; *Total Annual Hours:* 175.

To obtain copies of the supporting statement and any related forms for the proposed paperwork collections referenced above, access HCFA's Web Site address at http://www.hcfa.gov/regs/prdact95.htm, or E-mail your request, including your address, phone number, OMB number, and HCFA document identifier, to Paperwork@hcfa.gov, or call the Reports Clearance Office on (410) 786–1326. Written comments and recommendations for the proposed information collections must be mailed within 30 days of this notice directly to the OMB desk officer: OMB Human Resources and Housing Branch, Attention: Allison Eydt, New Executive Office Building, Room 10235, Washington, D.C. 20503.

Dated: June 2, 1998.

John P. Burke III,

HCFA Reports Clearance Officer, HCFA Office of Information Services, Information Technology Investment Management Group, Division of HCFA Enterprise Standards.

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