promoting safe flight of civil aircraft in air commerce by prescribing regulations for practices, methods, and procedures the Administrator finds necessary for safety in air commerce. This regulation is within the scope of that authority because it addresses an unsafe condition that is likely to exist or develop on products identified in this rulemaking action.

List of Subjects in 14 CFR Part 39

Air transportation, Aircraft, Aviation safety, Safety.

Adoption of the Amendment

■ Accordingly, pursuant to the authority delegated to me by the Administrator, the Federal Aviation Administration amends part 39 of the Federal Aviation Regulations (14 CFR part 39) as follows:

PART 39—AIRWORTHINESS DIRECTIVES

■ 1. The authority citation for part 39 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40113, 44701.

§ 39.13 [Amended]

■ 2. Section 39.13 is amended by adding a new airworthiness directive to read as follows:

2005–24–05 Boeing Vertol (Boeing): Amendment 39–14385. Docket No. FAA–2005–23085; Directorate Identifier 2005–SW–25–AD.

Applicability: Model 107–II helicopters, all serial numbers, with a quill shaft, part number (P/N) 107D2067, all dash numbers, and a spiral bevel pinion gear (pinion gear), P/N 107D2215, installed, certificated in any category.

Compliance: Required as indicated.

To detect a fatigue crack in a quill shaft to prevent separation of the quill shaft between the aft transmission and the mix box assembly, loss of rotor synchronization, and subsequent loss of control of the helicopter, accomplish the following:

(a) For a helicopter with a pinion gear installed with the following hours time-in-service (TIS):

Pinion gear hours TIS	Compliance time
700 or more hours TIS	Within 50 hours TIS, unless accomplished within the previous 350 hours TIS.
Less than 700 hours TIS	On or before reaching 750 hours TIS.

(1) Remove the aft transmission assembly, separate the mix box assembly from the aft transmission, and remove the quill shaft from the pinion gear assembly;

(2) Visually inspect the external spline of the quill shaft for a chipped or cracked tooth around the pinhole; and

(3) Magnetic particle inspect the quill shaft for a crack.

(b) Before further flight, replace any quill shaft that has a crack or a chipped or cracked tooth with an airworthy quill shaft.

Note 1: Boeing Service Bulletin No. 107–63–1005, Revision 1, dated April 27, 2005, pertains to the subject of this AD.

Note 2: Replacement quill shafts manufactured by Kawasaki Heavy Industries (KHI) for use on their Model KV107–II helicopters must be approved by the geographic Aircraft Certification Office (ACO) on a case-by-case basis for installation on a Boeing Model 107–II helicopter.

(c) To request a different method of compliance or a different compliance time for this AD, follow the procedures in 14 CFR 39.19. Contact the Manager, New York ACO, Engine and Propeller Directorate, FAA, for information about previously approved alternative methods of compliance.

(d) Special flight permits will not be issued.

(e) This amendment becomes effective on December 8, 2005.

Issued in Fort Worth, Texas, on November 16, 2005.

Scott A. Horn,

Acting Manager, Rotorcraft Directorate, Aircraft Certification Service.

[FR Doc. 05–23156 Filed 11–22–05; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 312

[Docket No. 2000N–1663]

RIN 0910–AA61

Investigational New Drugs: Export Requirements for Unapproved New Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations on the exportation of investigational new drugs, including biological products. The final rule describes four different mechanisms for exporting an investigational new drug product. These provisions implement changes in FDA's export authority resulting from the FDA Export Reform and Enhancement Act of 1996 and also simplify the existing requirements for exports of investigational new drugs.

DATES: This rule is effective December 23, 2005.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Office of Policy and Planning (HF–23), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0587.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of June 19, 2002 (67 FR 41642), we (FDA) published a proposed rule to describe various options for exporting an investigational new drug, including a biological product. We issued the proposed rule to implement statutory changes resulting from the FDA Export Reform and Enhancement Act of 1996 (Pub. L. 104–134, as amended by Pub. L. 104–180) and to modify a pre-existing regulatory program for exporting investigational new drugs.

Under current § 312.110(b) (21 CFR 312.110(b)), any person who intends to export an unapproved new drug product for use in a clinical investigation must have either an investigational new drug application (IND) or submit a written request to us (FDA). The written request must provide sufficient information about the drug to satisfy us 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 (see § 312.110(b)(2)(i)). The request must also specify the quantity of the drug to be shipped and the frequency of expected shipments (id.). If we authorize exportation of the drug, we notify the government of the importing country (id.). Similar procedures exist for export requests made by foreign governments (see § 312.110(b)(2)(ii)). Section 312.110(b)(3) states that the requirements in paragraph (b) apply only where the drug is to be used for the purpose of a clinical investigation. Section 312.110(b)(4) states that the requirements in paragraph (b) do not apply to the exports of new drugs approved or authorized for export under

section 802 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 382) or section 351(h)(1)(A) of the Public Health Service Act.

The program for exporting investigational new drugs is commonly known as the ''312 program'' because the regulation pertaining to the program is located in part 312 (21 CFR part 312). Between fiscal years 1994 and 1997, we received nearly 1,800 export requests under the 312 program. We found that very few requests (less than 1 percent) presented any public health concerns.

In 1996, the FDA Export Reform and Enhancement Act of 1996 became law. The FDA Export Reform and Enhancement Act created, among other things, two new provisions that affect the exportation of investigational drug products, including biological products. One provision, now section 802(b)(1)(A) of the act, authorizes exportation of an unapproved new drug to any country if that drug has valid marketing authorization by the appropriate authority in Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, the European Union (EU), or a country in the European Economic Area (EEA) and certain other requirements are met. These countries are listed in section 802(b)(1)(A)(i) and (b)(1)(A)(ii) of the act and are sometimes referred to as the ''listed countries.'' Currently, the EU countries are Austria, Belgium, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom. The EEA countries are the EU countries, and Iceland, Liechtenstein, and Norway. The list of countries in section 802(b)(1)(A)(i) of the act will expand automatically if any country accedes to the EU or becomes a member of the EEA. Exports under section 802(b)(1)(A) of the act can encompass exportation of an unapproved new drug product for investigational use in a foreign country if the exported drug product has marketing authorization in any listed country and the relevant statutory requirements are met. Exports under section 802(b)(1)(A) of the act do not require prior FDA authorization.

The second provision, now section 802(c) of the act, permits exportation of unapproved new drugs intended for investigational use to any listed country in accordance with the laws of that country. Exports of drugs to the listed countries under section 802(c) of the act do not require prior FDA authorization and are exempt from regulation under section 505(i) of the act (21 U.S.C. 355(i)).

All drug products exported under section 802 of the act are, however, subject to certain general requirements. Section 802(f) of the act prohibits export if the unapproved new drug:

- Is not manufactured, processed, packaged, and held in substantial conformity with current good manufacturing practice (CGMP) requirements;
- Is adulterated under certain provisions of section 501 of the act (21 U.S.C. 351);
- Does not comply with section 801(e)(1) of the act (21 U.S.C. 381(e)(1)), which requires that the exported product be intended for export, meet the foreign purchaser's specifications, not be in conflict with the laws in the importing country, be labeled on the outside of the shipping package that the products are intended for export, and not be sold or offered for sale in the United States;
- Is the subject of a determination by FDA that the probability of reimportation of the exported drug would present an imminent hazard to the public health and safety of the United States;
- Presents an imminent hazard to the public health of the foreign country;
- Fails to comply with labeling requirements in the country receiving the exported drug; or
- Is not promoted in accordance with labeling requirements in the importing country and, where applicable, in the listed country in which the drug has valid marketing authorization.

Section 802(g) of the act also imposes certain recordkeeping and notification obligations on drugs exported under section 802 of the act. In the **Federal Register** of December 19, 2001 (66 FR 65429), we issued a final rule on these recordkeeping and notification requirements, and the rule is codified at § 1.101 (21 CFR 1.101).

The new export provisions in section 802 of the act significantly reduced the number of requests under the 312 program from an annual average of 570 requests to 200 requests. This final rule amends § 312.110 to conform to the FDA Export Reform and Enhancement Act of 1996 and to modify the 312 program.

II. Comments on the Proposed Rule

A. What Did the Proposed Rule Cover? How Many Comments Did FDA Receive?

The proposed rule would amend § 312.110 to provide four mechanisms for exporting investigational new drugs, eliminate unnecessary language in the current regulation, and modify the export requirements for the 312 program. The proposed rule would not contain any new recordkeeping requirements because such records are already required under § 312.57 (if the foreign clinical trial is under an IND) or § 1.101.

We received eight comments on the proposed rule. The comments came from seven sources: A pharmaceutical trade association, four pharmaceutical companies, one consulting firm, and one university student. In general, six comments strongly supported the rule with few or no modifications. One comment opposed exports of investigational new drugs generally, and another comment sought clarification of one statutory provision and did not address the rule itself. We address most comments in greater detail below. (We do not discuss the comment seeking a clarification of the statute because it was not directly related to the rule.) To make it easier to identify comments and our responses, the word ''Comment,'' in parenthesis, will appear before the comment's description, and the word ''Response,'' in parenthesis, will appear before our response. We have also numbered each comment to identify them more easily. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which it was received.

B. Can Investigational New Drugs Be Exported Under an IND?

Proposed § 312.110(b)(1) would represent the first mechanism for exporting an investigational new drug and would apply if the foreign clinical investigation is to be done under an IND. Proposed § 312.110(b)(1) would provide that an investigational new drug may be exported from the United States if an IND is in effect for the drug under § 312.40, the drug complies with the laws of the country to which it is being exported, and each person who receives the drug is an investigator who will use the drug in a study submitted to and allowed to proceed under the IND. Because this provision is not limited to particular countries, a drug that is the subject of an IND could be exported under the act to any country in the world if the export is for the purpose of conducting a clinical investigation in the importing foreign country. Exporters should be aware, however, that this provision, like all provisions in proposed § 312.110, pertain only to the requirements of the act. Other Federal laws, such as those relating to customs or controlled substances or barring

exports to specific countries, may restrict or prohibit an export even if it would be permitted under this rule.

We received no comments on this provision and have finalized it without change.

C. Can Investigational New Drugs Be Exported If They Have Marketing Authorization? Which Countries Must Provide That Marketing Authorization?

Proposed § 312.110(b)(2) would represent the second mechanism for investigational new drug exports and would implement section 802(b)(1) of the act with respect to exports of unapproved new drugs for investigational use (although section 802(b)(1) of the act has been in effect since April 1996). Under the proposal, if a drug product that is not approved for use in the United States has valid marketing authorization in Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or in any country in the EU or the EEA, the drug may be exported for any use, including investigational use, to any country, provided that the export complies with all applicable requirements pertaining to exports. Prior FDA approval to export the drug would not be required, nor would proposed § 312.110(b)(2) require the drug to be the subject of an IND. The exporter and the exported products, however, would have to comply with the foreign country's laws and with requirements in section 802(f) and (g) of the act. The proposal would also require compliance with the export notification and recordkeeping requirements § 1.101.

We received no comments on this provision and have finalized it without change.

However, regarding the export notification and recordkeeping requirements at § 1.101, we note that we received a petition for reconsideration that challenges, among other things, the recordkeeping requirement at § 1.101(b)(2). Section 1.101(b)(2) describes the records that may be kept to show that an export does not conflict with a foreign country's laws, as required by section 801(e)(1)(B) of the act. Section 1.101(b)(2) states that the records may consist of a letter from an appropriate foreign government agency stating that the product has marketing approval from the foreign government or does not conflict with the foreign country's laws or a notarized certification by a responsible company official in the United States that the product does not conflict with the foreign country's laws. In a letter dated July 22, 2002, we informed the petitioner that we would exercise enforcement discretion regarding the letter and certification described in § 1.101(b)(2), that parties must still comply with the statutory requirement in section 801(e)(1)(B) of the act, and that we would be evaluating whether to issue an advance notice of proposed rulemaking regarding the petitioner's issues (see Letter from Margaret M. Dotzel, Associate Commissioner for Policy, to Peter Barton Hutt, Covington & Burling, dated July 22, 2002; this letter can be found in FDA Docket No. 1998N–0583). We subsequently issued an advance notice of proposed rulemaking regarding the issues raised by the petitioner (see 69 FR 30842, June 1, 2004) and are continuing to evaluate the comments. We are continuing to exercise enforcement discretion regarding § 1.101(b)(2), but we remind would-be exporters that they must continue to comply with the statutory requirement in section 801(e)(1)(B) of the act and the remaining provisions in § 1.101.

D. Can Investigational New Drugs Be Exported Directly to Certain Countries Without FDA Approval?

Proposed § 312.110(b)(3), the third mechanism for investigational new drug exports, would implement section 802(c) of the act with respect to exports of unapproved new drugs for investigational use (although section 802(c) of the act has been in effect since April 1996). In brief, under proposed § 312.110(b)(3), if an unapproved drug is to be exported for investigational use to any listed country in accordance with the laws of that country, then no prior FDA authorization would be required. Exports of a drug for investigational use under proposed § 312.110(b)(3) would have to comply with the foreign country's laws and the applicable statutory requirements in section 802(c), (f), and (g) of the act. Proposed § 312.110(b)(3) would also require compliance with the relevant recordkeeping requirements at § 1.101.

Proposed § 312.110(b)(3) would add that investigational new drugs that are not under an IND and are exported under section 802(c) of the act do not have to bear a label stating, ''Caution: New Drug-Limited by Federal (or United States) law to investigational use.'' This proposed requirement reflected the fact that the label statement is required under section 505(i) of the act, and that, absent an IND, drugs exported under section 802(c) of the act are not subject to section 505(i) of the act.

The preamble to the proposed rule discussed our interpretation of section 802(c) of the act and the issue of ''transshipment.'' ''Transshipment'' refers to the practice of shipping a product to a country from which it will later be shipped to another country. We stated that we were aware that some firms have interpreted section 802(c) of the act as permitting transshipment to unlisted countries as long as the shipment went through a listed country (see 67 FR 41642 at 41643). (We knew about the firms' position on transshipment from comments we had received on a draft export guidance document that appeared in the **Federal Register** of June 12, 1998 (63 FR 32219).) We noted that section 802(c) of the act is silent with respect to transshipment, and a more reasonable interpretation is that the provision does not allow transshipments. We added that interpreting section 802(c) of the act to allow transshipment would be inconsistent with our traditional practice under § 312.110 and would presume, in the absence of any supporting language in the statute or its legislative history, that the listed countries may serve as mere transfer points or conduits for investigational new drugs and devices destined for unlisted countries (67 FR 41642 at 41643).

Nevertheless, because we knew that some firms insisted that section 802(c) of the act allows transshipment, the preamble to the proposed rule stated that we would interpret section 802(c) of the act as permitting investigational new drugs to be sent to principal investigators in a listed country who then use the investigational new drug in an unlisted country, provided that the principal investigator conducts the clinical investigations in accordance with the requirements of both the listed country and the unlisted country where the investigation is conducted. For example, if firm A exported an investigational new drug to principal investigator X in Norway (a listed country), we stated that we would interpret section 802(c) of the act as permitting exportation of the investigational new drug, without prior FDA authorization, as long as firm A and the exported drug met all other statutory conditions pertaining to the exportation. Principal investigator X could then administer the investigational new drug in an unlisted country so long as principal investigator X conducted the clinical investigation in accordance with Norwegian requirements and any requirements in the unlisted country where the investigational new drug is administered.

(Comment 1) Three comments disagreed with this limited transshipment position. The comments acknowledged that the law is subject to

various interpretations, but argued against allowing transshipment from listed countries to unlisted countries. The comments explained that a clinical investigator may have little ability to control how a drug is moved, stored, or used ''if he or she is not supported by the laws of the land'' and so expecting the clinical investigator ''to enforce the laws, regulations and practices of the listed country in the unlisted country (even assuming there are no contradictions between them) is, we believe, quite unrealistic and exposes the investigator, the sponsor and, not least, the patients to significant risks.'' Consequently, two comments recommended that we not allow transshipment from listed countries to unlisted countries. Another comment stated that we should not allow transshipment from listed countries to unlisted countries, but then stated that transshipment of investigational new drugs should be ''the responsibility of the sponsor alone.''

(Response) We have reconsidered our interpretation of section 802(c) of the act and agree that transshipment should not be permitted under section 802(c) of the act. Although our limited transshipment policy was intended to accommodate the industry, we agree with the pharmaceutical industry comments that a clinical investigator's ability to apply a listed country's laws and regulations in an unlisted country may be difficult at best. Therefore, we do not interpret section 802(c) of the act or § 312.110(b)(3) as allowing transshipment from listed countries to unlisted countries.

Furthermore, we do not agree that transshipment should be the sponsor's responsibility alone because that would mean that a sponsor could consider itself free to transship an investigational new drug regardless of our interpretation of section 802(c) of the act.

As for proposed § 312.110(b)(3) itself, we received no comments on the provision and have finalized it without change.

E. What Changes Are Being Made to the ''312 Program?''

Proposed § 312.110(b)(4) would represent the fourth mechanism for exporting an investigational new drug and would pertain to unapproved new drugs exported to any country for investigational use without an IND, and we expected that the provision would be used by persons who intend to export a drug that does not have valid marketing authorization from a listed country for investigational use to an unlisted country. Proposed § 312.110(b)(4) would modify the 312 program by eliminating the requirement of prior FDA authorization. The proposal would require a person seeking to export an unapproved new drug for investigational use without an IND to send a written certification to us. The certification would be submitted at the time the drug is first exported and would describe the drug being exported (i.e., trade name (if any), generic name, and dosage form), identify the country or countries to which it is being exported, and affirm that various conditions or criteria had been met, such as:

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

The preamble to the proposed rule explained that we were proposing to accept certifications because our experience with the 312 program indicated that very few investigational new drug exports under the existing program raise any public health concerns. The certification would eliminate the requirement of prior FDA authorization of a request to export a drug for investigational use (67 FR 41642 at 41644). Additionally, by conditioning exports to unlisted countries under the 312 program on the conduct of clinical investigations in accordance with § 312.120, the use of investigational new drugs under the 312 program would be subject to internationally recognized requirements for clinical investigations (id. at 41645). The proposal would also require the exporter of the investigational new drug to retain records showing its compliance with the provision's requirements.

(Comment 2) Several comments expressed strong support for streamlining the 312 program. For example, one comment called the proposal a ''bold but considered move'' that would reduce administrative burdens on FDA and sponsors without waiving any significant obligations.

Three comments questioned why proposed § 312.110(b)(4)(xii) would require the exporter to certify that the investigational new drug ''is promoted in accordance with its labeling.'' The comments said that the requirement is unnecessary because investigational new drugs are not the subject of promotion and requested that we clarify or delete the requirement.

(Response) We agree with the comments that investigational new drugs are not to be promoted, and we have deleted the language regarding promotion from § 312.110(b)(4).

However, one comment's claim that proposed § 312.110(b)(4) would reduce administrative burdens without waiving any significant obligations prompted us to consider whether a person exporting a drug under § 312.110(b)(4) should be able to export an investigational new drug in an emergency without satisfying certain criteria. For example, in recent years, we have seen growing concern over the possible use of biological, chemical, or other weapons in a terrorist attack. These concerns have prompted interest by some foreign countries in stockpiling drugs and biological products for possible use if such an attack occurs. We have also seen the sudden emergence of new diseases, such as Severe Acute Respiratory Syndrome (SARS), and can foresee situations where a foreign country might seek importation of an investigational new drug to respond to a sudden and immediate disease outbreak. In such situations, the need to stockpile drugs or to provide potentially helpful treatment quickly to a large number of patients may be incompatible with certain criteria in § 312.110(b)(4).

Therefore, the final rule includes a new § 312.110(b)(5) to address the exportation of investigational new drugs due to a national emergency in a foreign country. New § 312.110(b)(5) contemplates two different national emergency scenarios. The first scenario, at § 312.110(b)(5)(i), provides for exportation of an investigational new drug in a foreign country to be stored for possible use if and when a national emergency in that foreign country arises. Under § 312.110(b)(5)(i), a person may export the investigational new drug under § 312.110(b)(4) and may exclude

from its certification an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), and/or (b)(4)(ix), provided that he or she:

- Provides a written statement, under § 312.110(b)(5)(i)(A)(*1*), explaining why compliance with each such paragraph is not feasible or is contrary to the best interests of the individuals who may receive the investigational new drug;
- Provides a written statement from an authorized official of the importing country's government. The statement must attest that the official agrees with the exporter's statement made under § 312.110(b)(5)(i)(A)(*1*); explain that the drug is to be stockpiled solely for use of the importing country in a national emergency; and describe the potential national emergency that warrants exportation of the investigational new drug under this provision; and
- Provides a written statement showing that the Secretary of Health and Human Services (the Secretary), or his or her designee, agrees with the findings of the authorized official of the importing country's government.

We decided that in a national emergency, ''stockpiling'' scenario, exporters should be able to drop the affirmations in paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), and/or (b)(4)(ix) from their certifications if, due to the potential national emergency for which the drug is being stockpiled, compliance with that paragraph is infeasible or contrary to the best interests of the individuals who may receive the investigational new drug. For example, several foreign governments have asked for our help in exporting investigational vaccines to their countries to reduce their citizens' vulnerability to a certain pathogen. Vaccine production is very complex, so it is unlikely that a manufacturer could respond quickly to a large-scale national emergency in a foreign country. Thus, if we were to insist that all investigational vaccines exported in a national emergency scenario be ''intended for export'' (as otherwise required by § 312.110(b)(4)(i)), vaccines that had been intended for domestic use could not be exported to address a national emergency in a foreign country because those vaccines would not have been ''intended for export'' when they were first made. Providing for the deletion of the ''intended for export'' requirement in a national emergency, stockpiling scenario makes it possible to export products originally intended for domestic use to meet a more important foreign need.

In the national emergency, ''stockpiling'' scenario, exportation may not proceed without prior FDA authorization. We decided to require FDA authorization to ensure that exportation of a drug based on this scenario is limited to the requirements set out in § 312.110(b)(5)(i) and not used for other situations for which other regulatory requirements apply.

The second national emergency scenario is at § 312.110(b)(5)(ii). This provision would apply where the national emergency is both sudden and immediate. For example, § 312.110(b)(5)(ii) could be used when a bioterrorist attack has occurred in a foreign country and has created an immediate need to export an investigational new drug for use in the foreign country. It could also apply where the national emergency is imminent, but has not yet occurred. For example, § 312.110(b)(5)(ii) might be applicable where a foreign government has evidence showing that a particular novel disease outbreak is about to occur and that prompt administration of an investigational new drug is needed to treat or immunize its citizens before the disease assumes epidemic proportions. Thus, in these examples, the words ''sudden'' and ''immediate'' are meant to convey a sense that the national emergency resulted from unforeseen circumstances and that the exported drug is needed quickly in order to address the national emergency, and we expect § 312.110(b)(5)(ii) to be used in very rare circumstances. In other words, § 312.110(b)(5)(ii) should not be used in situations where a person simply wants to export a drug to address longstanding public health concerns (such as a disease which is and has been prevalent in the foreign country for years).

Under § 312.110(b)(5)(ii), a person may export an investigational new drug under § 312.110(b)(4) and exclude from its certification an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(v), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), (b)(4)(ix), and/or (b)(4)(xi), provided that he or she:

- Provides a written statement, under § 312.110(b)(5)(ii)(A)(*1*), explaining why compliance with each such paragraph is not feasible or is contrary to the best interests of the individuals who are expected to receive the investigational new drug; and
- Provides sufficient information from an authorized official of the importing country's government to enable the Secretary, or his or her designee, to decide whether a national emergency has developed or is developing in the importing country, whether the investigational new drug will be used solely for that national emergency, and whether prompt exportation of the investigational new drug is necessary.

We decided that, in the case of a sudden and immediate national emergency in a foreign country, the exporter's certification may omit an affirmation addressing paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(v), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), (b)(4)(ix) and/or (b)(4)(xi) if, due to the sudden and immediate national emergency, compliance with that paragraph or paragraphs are infeasible or contrary to the best interests of the individuals who may receive the investigational new drug. For example, it would not be necessary to insist that the exported drug be labeled in accordance with the foreign country's laws where the foreign country itself had agreed that compliance with its labeling requirements was unnecessary during the national emergency.

Additionally, in contrast to the ''stockpiling'' scenario in § 312.110(b)(5)(i), exportation to meet a sudden and immediate national emergency may not proceed until the Secretary has decided whether a national emergency has developed or is developing in the importing country, whether the investigational new drug will be used solely for that national emergency, and whether prompt exportation of the investigational new drug is necessary. We reiterate that, given its reference to a ''sudden and immediate'' national emergency, § 312.110(b)(5)(ii) should be very rarely used.

Persons who wish to obtain a written statement from the Secretary under § 312.110(b)(5)(i) or to request that the Secretary make the determinations under § 312.110(b)(5)(ii) should direct their requests to: Secretary's Operations Center, Office of Emergency Operations and Security Programs, Office of Public Health Emergency Preparedness, Office of the Secretary, Department of Health and Human Services, 200 Independence Ave. SW., Washington, DC 20201.

Requests may be also be sent by FAX: 202–619–7870 or by e-mail: *HHS.SOC@hhs.gov*.

To complement these changes, we have revised § 312.110(c)(4) to state that exportation is not allowed under § 312.110(b)(4) if the conditions underlying the certification or the statements submitted under § 312.110(b)(5) are no longer met.

(Comment 3) One comment appeared to inquire whether transshipment could occur under the 312 program. The comment suggested that transshipment should be allowed if the sponsor amended its ''certification'' requesting shipment of an investigational new drug

from either a listed or unlisted country to another unlisted country ''where the protocol is unchanged and all applicable laws are met.'' The comment added that only products under the sponsor's direct control would be permitted for transshipment.

(Response) The comment may have misinterpreted the rule. Exports of an investigational new drug to a listed country fall within section 802(c) of the act and § 312.110(b)(3), and no certification is required. Consequently, if an investigational new drug is exported to a listed country under section 802(c) of the act, there is no ''certification'' to amend, and, as our response to comment 1 of this document stated, we will not interpret section 802(c) of the act as allowing transshipment from a listed country to an unlisted country.

As for exports under the 312 program and § 312.110(b)(4), we concede that our proposed revision of the 312 program did not prohibit its use for exports to listed countries. However, if a sponsor decided to use § 312.110(b)(4) to export an investigational new drug to a listed country, it would create unnecessary work for itself because, under § 312.110(b)(3), it could export the investigational new drug to the listed country without providing any documentation to us.

If the comment sought to use § 312.110(b)(4) to export an investigational new drug to an unlisted country and then transship that drug to another unlisted country, we would agree that § 312.110(b)(4) could be used, but only if both unlisted countries are identified in the original certification to us. In other words, the original certification would have to state that the investigational new drug is being sent to one unlisted country and then shipped to another unlisted country. We do not intend to permit sponsors to use § 312.110(b)(4) to ship investigational new drugs to an unlisted country and, at some later, unspecified date, amend the certification in the manner described by the comment. We are concerned that allowing amendments to certifications that would change the country receiving the exported drug would enable an unscrupulous person to avoid several critical obligations, particularly those that are specific to the receiving country, such as ensuring that:

- The clinical investigation will be conducted in accordance with § 312.120;
- The drug meets the foreign purchaser's or consignee's specifications; and
- The drug does not present an imminent hazard to the public health in the foreign country.

Given these concerns, we decline to revise the rule to allow amended certifications under § 312.110(b)(4) that would enable sponsors to transship investigational new drugs without observing several important obligations in § 312.110(b)(4) itself.

F. Are There Any Restrictions on Investigational New Drug Exports?

Proposed § 312.110(c) would prohibit exports under certain conditions. For example, for drugs under an IND that are exported under proposed 312.110(b)(1), exportation would not be allowed if the IND is no longer in effect. For drugs exported under proposed § 312.110(b)(2), (b)(3), or (b)(4), exportation would not be allowed if the requisite conditions underlying or authorizing the exportation are no longer met. For all investigational new drugs exported under proposed § 312.110, exportation would not be allowed if the drug no longer complied with the laws of the importing country.

We received no comments on this provision. However, as explained in section II.E of this document, we have created a § 312.110(b)(5) to address exportation of investigational new drugs to meet national emergencies in a foreign country. This new provision establishes new conditions on the export requirements under § 312.110(b)(4) in such national emergencies. Consequently, we have revised § 312.110(c)(4) to state that exportation is not allowed under § 312.110(b)(4) if the conditions underlying the certification or the statements submitted under § 312.110(b)(5) are no longer met.

G. What Other Changes Did FDA Propose?

The proposed rule would also make several minor amendments to reflect or update statutory requirements and to redesignate paragraphs (to accommodate other proposed changes). In brief, the proposal would:

- Redesignate § 312.110(b)(4) as new § 312.110(d) to state that the export requirements in § 312.110 do not apply to insulin or to antibiotic drug products exported for investigational use. This provision would reflect section 802(i) of the act which provides that insulin and antibiotics may be exported in accordance with the export requirements in section 801(e)(1) of the act without complying with section 802 of the act.
- Eliminate a potentially confusing and incorrect reference to new drugs ''* * *approved or authorized for export under section 802 of the act * * * or section 351(h)(1)(A) of the Public Health Service Act'' because the FDA Export Reform and Enhancement Act eliminated most FDA approval requirements for exported drugs. As for section 351(h) of the Public Health Service Act, it pertains to exports of partially processed biological products that are: (1) Not in a form applicable to the prevention, treatment, or cure of diseases or injuries of man; (2) not intended for sale in the United States; and (3) intended for further manufacture into final dosage form outside the United States. Thus, partially processed biological products exported under section 351(h) of the Public Health Service Act are not exported for investigational use, so they do not have to be mentioned in § 312.110. We also noted that the FDA Export Reform and Enhancement Act of 1996 revised and renumbered section 351(h) of the Public Health Service Act, and so the revised section no longer contains a paragraph (h)(1)(A) (see 67 FR 41642 at 41645).
- Amend the authority citation for part 312 to reflect additional statutory provisions, such as sections 801, 802, 803, and 903 of the act (21 U.S.C. 381, 382, 383, and 393), that affect investigational new drug exports, FDA's international activities, and rulemaking.
- Remove the text at § 312.110(b)(3) stating that the export requirements in § 312.110(b) apply only where the drug is to be used for the purpose of a clinical investigation. We proposed to delete this language because the proposed rule expressly refers to exports of investigational new drugs for use in clinical investigations.

We received no comments on these provisions or changes and have finalized them without change.

H. What Other Comments Did FDA Receive?

Several comments responded to specific questions we had presented in the preamble to the proposed rule or discussed other issues related to the export of investigational new drugs or the conduct of foreign clinical trials.

The preamble to the proposed rule noted that section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)) directs the Secretary to establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions (67 FR 41642 at 41645). We invited comment on whether we should make available information on clinical trials involving investigational new drugs exported under proposed § 312.110(b)(4).

(Comment 4) Some comments opposed making information on drugs exported under proposed § 312.110(b)(4) publicly available. The comments argued that section 402(j) of the Public Health Service Act was intended to provide clinical trial information to American patients and that we had no legal authority to collect or disclose information on foreign clinical trials.

(Response) We agree with the comments that section 402(j) of the Public Health Service Act does not apply to exports under § 312.110(b)(4), but disagree as to the rationale. Section 402(j) of the Public Health Service Act refers to ''clinical trials'' without any express requirement that the clinical trials be conducted in the United States. However, we believe that this provision only applies to clinical trials conducted under an IND.

The Senate Committee on Labor and Human Resources' report on the ''Food and Drug Administration Modernization and Accountability Act of 1997'' describes the data bank as requiring sponsors of clinical trials to provide certain clinical trial information to the National Institutes of Health ''not later than 21 days after the approval by the FDA'' (see S. Rept. 105–43, ''Food and Drug Administration Modernization and Accountability Act of 1997,'' 105th Cong., 1st sess. at p. 99 (July 1, 1997)). The report apparently meant not later than 21 days after the IND goes into effect since, strictly speaking, FDA does not ''approve'' clinical trials or INDs. Rather, an IND goes into effect after 30 days if FDA does not notify the sponsor that the trials are subject to a clinical hold before then, or earlier than 30 days if FDA so notifies the sponsor that the trials may begin. Nonetheless, this statement strongly suggests that only trials that are conducted under an IND are to be included in the data bank. Therefore, based on this legislative history, we do not interpret section 402(j) of the Public Health Service Act as applying to exports under § 312.110(b)(4).

(Comment 5) One comment focused on the proposed rule's cross-references to statutory provisions. The comment said that the cross-references ''greatly complicate the reading and practical understanding of the regulation'' and suggested that we incorporate the statutory language directly into the rule.

(Response) We decline to amend the rule as suggested by the comment. While we understand that cross-references in a regulation can make it more difficult to read and to understand a particular requirement, there are several practical reasons for not inserting statutory language into a rule. First, several of the cited statutory provisions contain cross-references themselves. Section 802(f) of the act, which is mentioned in § 312.110(b)(2), (b)(3), (c)(2), and (c)(3), refers to certain adulteration provisions in section 501 of the act and to export requirements at section 801(e)(1) of the act. Thus, inserting statutory language into the rule would still result in cross-references to other statutory provisions. Second, if we were to use statutory language in the rule and if Congress amended that particular statute later, we would be obliged to begin new rulemaking to reflect the new statutory language, even if the revised statutory language had no significant impact on the rule itself. Otherwise, the regulation would be inconsistent with the act, and differences between the act and the regulatory language could result in needless disagreements or disputes. Third, inserting statutory language into a rule would make the rule much longer and have limited value because a firm should be conscious of both statutory and regulatory requirements. In general, we may issue a regulation to describe our interpretation of a particular statutory requirement and to create a consistent, enforceable obligation on affected parties and on the agency itself. If a particular statutory provision is self-executing or self-explanatory, we may feel that no regulation is necessary. Given these considerations, we decline to insert the statutory language into the rule.

(Comment 6) One comment opposed the rule entirely. The comment questioned why a foreign country would accept a drug that could not be used in the United States and alleged that companies exported investigational new drugs to avoid breaking U.S. law and to ''exploit people in other countries.'' The comment suggested that companies supporting the proposed rule ''should be investigated for unethical conduct.''

(Response) We disagree with the comment. The mechanisms for exporting an investigational new drug reflect statutory provisions in sections 505(i), 802(b)(1), and 802(c) of the act. As a result, contrary to the comment's assertion, firms exporting a drug for investigational use in a foreign country in accordance with this rule would be acting in compliance with the act. Given that fact, we have no basis for attributing an improper or unethical motive to those who would export such products or those who support this rulemaking.

(Comment 7) Several comments, in discussing their position against transshipment, recommended that we ''work diligently to approve unlisted countries and add them to the listed countries.''

(Response) We interpret the comments' suggestion of ''adding'' countries as referring to section 802(b)(1)(B) of the act, which states that the Secretary ''may designate an additional country to be included in the list of countries described in [section 802(b)(1)(A) of the act]'' if certain requirements are met. However, section 802(b)(1)(B) of the act also states that the authority to add countries to the list cannot be delegated. As a result, FDA has no authority or ability to add countries to the list.

We note that, since the FDA Export Reform and Enhancement Act became law in 1996, we have not received any substantive inquiries about adding a particular country to the group of listed countries. We are not aware of any similar inquiries to the Department of Health and Human Services.

III. Description of the Final Rule

The final rule is substantially similar to the proposed rule as it describes four mechanisms for exporting a drug, including a biological product, for investigational use. The four mechanisms are: (1) Exporting an investigational new drug under an IND, where the foreign clinical trial is covered in the IND; (2) exporting an investigational new drug that has valid marketing authorization from a ''listed country'' identified in section 802(b)(1)(A) of the act; (3) exporting an investigational new drug to a listed country; or (4) providing a certification to FDA and exporting the investigational new drug under a modified ''312 program.'' In the latter case, the final rule also identifies the certification criteria that must be followed if the export is to occur under the 312 program.

To recap the principal features of each export mechanism,

1. Section 312.110(b)(1) could be used where the foreign clinical trial is the subject of an IND.

2. Section 312.110(b)(2) could be used where the investigational new drug has received market authorization in any ''listed country'' and complies with the laws of the country to which it is being exported.

3. Section 312.110(b)(3) could be used when the investigational new drug is to be used in a clinical investigation in a ''listed country.''

4. Section 312.110(b)(4) could be used in situations not covered by § 312.110(b)(1), (b)(2), or (b)(3), and the requirements in § 312.110(b)(4) may be streamlined or modified in the event of

a national emergency in a foreign country (see § 312.110(b)(5)).

Please note that the export mechanisms are not mutually exclusive. For example, if a sponsor obtains an IND for a clinical investigation in a listed country, the sponsor is not obliged to export the investigational new drug under § 312.110(b)(2) or (b)(3).

The final rule also describes the conditions under which exportation may not occur. In general, these conditions are: (1) When the export no longer complies with the statutory requirements that would allow the drug to be exported; (2) when the conditions underlying the certification in the 312 program are no longer met; or (3) when the exported investigational new drug no longer complies with the foreign country's laws.

The final rule also states that insulin and antibiotics may be exported for investigational use in accordance with section 801(e)(1) of the act. The act specifically states that exports of insulin and antibiotics that are not approved for use by FDA are subject only to section 801(e)(1) of the act.

IV. Legal Authority

Section 505(i) of the act authorizes the agency to issue regulations pertaining to drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Under this authority, FDA has, for many years, approved the export of certain unapproved new drugs for investigational use in one or more foreign countries. Additionally, FDA can, under its general authority over investigational new drugs, terminate an IND under certain conditions.

The final rule is consistent with section 505(i) of the act insofar as § 312.110(b)(1) pertains to drugs that are the subject of an IND and § 312.110(b)(4) requires clinical investigations involving an investigational new drug without an IND that is exported to a foreign country to be conducted in accordance with § 312.120. Section 505(i) of the act also gives FDA express authority to issue regulations pertaining to investigational new drugs.

The final rule also implements section 802 of the act, which applies to unapproved drug products intended for export. Section 802(c) of the act applies to exports of unapproved drug products intended for investigational use. As stated earlier, section 802(c) of the act permits the export of a drug or device intended for investigational use to Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or any country in the EU or EEA in accordance with the laws of the importing country. No prior FDA authorization is required, and exports under section 802(c) of the act are also exempt from regulation under section 505(i) of the act. However, section 802(f) of the act prohibits export of a drug if certain conditions are not met (such as conformity with CGMPs, compliance with requirements contained in section 801(e)(1) of the act, and not being adulterated under certain provisions of section 501 of the act). Section 312.110(b)(3) pertains to exports of investigational new drugs to listed countries, under section 802(c) of the act. Additionally, § 312.110(b)(2) pertains to drugs exported under section 802(b) of the act and requires that such exports comply with section 802(f) of the act.

Authority to issue regulations to implement section 802 of the act, and for the efficient enforcement of the act generally, is contained in section 701(a) of the act (21 U.S.C. 371(a)). Section 903 of the act also provides general powers for implementing policies respecting FDA programs and activities. Thus, the final rule implements sections 505(i) and 802 of the act. Furthermore, it is also authorized under our rulemaking authorities at sections 505(i) and 701(a) of the act, and FDA's general authority at section 903 of the act.

V. Environmental Impact

FDA has determined under 21 CFR 25.30(h) and (i), and 25.31(e) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VII. Paperwork Reduction Act of 1995

This final rule contains information collection provisions requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these provisions is given below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Investigational New Drug Applications: Export Requirements for Unapproved New Drug Products.

Description: The final rule provides four different mechanisms for exporting an investigational new drug. First, an investigational new drug may be exported under an IND to any country if the IND covers the foreign clinical trial. Second, an investigational new drug that has received valid marketing authorization from a listed country may be exported for investigational use in any country subject to certain conditions (such as being in substantial conformity with CGMPs). Third, an investigational new drug may be exported to any listed country without prior FDA authorization for use in a clinical investigation, but would be subject to certain conditions (such as being in substantial conformity with CGMPs). Fourth, an investigational new drug may be exported provided that the sponsor submits a certification that the drug meets certain export criteria at the time the drug is exported. The final rule also requires persons exporting an investigational new drug under either the second, third, or fourth mechanisms to maintain records documenting their compliance with statutory and regulatory requirements.

Description of Respondents: Businesses.

TABLE 1.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
312.110(b)(2) and (b)(3)	370	1	370	3	1,110
312.110(b)(4)	200	1	200	1	200
Total					1,310

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 2.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
312.110(b)(4)	200	1	200	12	2,400
Total					2,400

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

The estimates are based on average export submissions in previous years and on information supplied by industry sources. For the recordkeeping requirement in § 312.110(b)(2) and (b)(3), FDA used the average annual number of export requests in previous years before enactment of the FDA Export Reform and Enhancement Act (approximately 570) and subtracted the number of export requests that it currently receives under the 312 program (200) to obtain an estimated 370 recordkeepers. These records, in general, would be subject to § 1.101 (66 FR 65429), and the estimated burden hours for the relevant parts of § 1.101 total 3 hours. Thus, the total record burden hours for § 312.110(b)(2) and (b)(3) would be 1,110 hours (370 records multiplied by 3 hours per record).

For § 312.110(b)(4), industry sources indicated that most firms already maintain records to demonstrate their compliance with export requirements, so the agency assigned a value of 1 hour for each response. The total recordkeeping burden for § 312.110(b)(4), therefore, is 200 hours (200 records multiplied by 1 hour per record).

Thus, the total recordkeeping burden would be 1,310 hours (1,110 + 200 = 1,310). Of this recordkeeping burden, 1,110 hours would be a statutory burden (because section 802(g) of the act requires persons exporting drugs under section 802 of the act to maintain records of alldrugs exported and the countries to which they were exported).

For the reporting requirement in § 312.110(b)(4), FDA's experience under the 312 program suggests that extremely few reports would be submitted. Assuming that 200 requests are received (the current number of requests under the 312 program) and that the reporting burden remains constant at approximately 12 hours per response, the total burden under § 312.110(b)(4) would be 2,400 hours. The reporting burden would be a regulatory (rather than statutory) burden.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this final rule to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VIII. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant impact on small entities, the agency must analyze regulatory options that would minimize the impact of the rule on small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

The agency has reviewed this final rule and determined that it is consistent with the regulatory philosophy and the principles identified in the Executive Order 12866 and these two statutes, as it will not result in an expenditure of $100 million or more in any one year. Because the rule raises novel policy issues, OMB has determined that this final rule is a significant regulatory action as defined under paragraph 4 of section 3(f) of Executive Order 12866.

The final rule facilitates exports of unapproved new drug products for use in clinical investigations in foreign countries by eliminating the need to submit requests for permission to export the drugs and to receive FDA authorization. This change reduces the cost to the affected small firms. Thus, the agency certifies that this final rule does not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

Because the final rule does not impose any mandates on State, local, or tribal governments, or the private sector

that will result in an expenditure of $100 million or more in any one year, FDA is not required to perform a cost-benefit analysis under the Unfunded Mandates Reform Act of 1995.

List of Subjects in 21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 312 is amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

■ 1. The authority citation for 21 CFR part 312 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 371, 381, 382, 383, 393; 42 U.S.C. 262.

■ 2. Section 312.110 is amended by revising paragraph (b) and by adding paragraphs (c) and (d) to read as follows:

§ 312.110 Import and export requirements.

* * * * *

(b) *Exports.* An investigational new drug may be exported from the United States for use in a clinical investigation under any of the following conditions:

(1) An IND is in effect for the drug under § 312.40, the drug complies with the laws of the country to which it is being exported, and each person who receives the drug is an investigator in a study submitted to and allowed to proceed under the IND; or

(2) The drug has valid marketing authorization in Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or in any country in the European Union or the European Economic Area, and complies with the laws of the country to which it is being exported, section 802(b)(1)(A), (f), and (g) of the act, and § 1.101 of this chapter; or

(3) The drug is being exported to Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or to any country in the European Union or the European Economic Area, and complies with the laws of the country to which it is being exported, the applicable provisions of section 802(c), (f), and (g) of the act, and § 1.101 of this chapter. Drugs exported under this paragraph that are not the subject of an IND are exempt from the label requirement in § 312.6(a); or

(4) Except as provided in paragraph (b)(5) of this section, the person exporting the drug sends a written certification to the Office of International Programs (HFG–1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, at the time the drug is first exported and maintains records documenting compliance with this paragraph. The certification shall describe the drug that is to be exported (i.e., trade name (if any), generic name, and dosage form), identify the country or countries to which the drug is to be exported, and affirm that:

(i) The drug is intended for export;

(ii) The drug is intended for investigational use in a foreign country;

(iii) The drug meets the foreign purchaser's or consignee's specifications;

(iv) The drug is not in conflict with the importing country's laws;

(v) The outer shipping package is labeled to show that the package is intended for export from the United States;

(vi) The drug is not sold or offered for sale in the United States;

(vii) The clinical investigation will be conducted in accordance with § 312.120;

(viii) The drug is manufactured, processed, packaged, and held in substantial conformity with current good manufacturing practices;

(ix) The drug is not adulterated within the meaning of section 501(a)(1), (a)(2)(A), (a)(3), (c), or (d) of the act;

(x) The drug does not present an imminent hazard to public health, either in the United States, if the drug were to be reimported, or in the foreign country; and

(xi) The drug is labeled in accordance with the foreign country's laws.

(5) In the event of a national emergency in a foreign country, where the national emergency necessitates exportation of an investigational new drug, the requirements in paragraph (b)(4) of this section apply as follows:

(i) *Situations where the investigational new drug is to be stockpiled in anticipation of a national emergency.* There may be instances where exportation of an investigational new drug is needed so that the drug may be stockpiled and made available for use by the importing country if and when a national emergency arises. In such cases:

(A) A person may export an investigational new drug under paragraph (b)(4) of this section without making an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), and/or (b)(4)(ix) of this section, provided that he or she:

(*1*) Provides a written statement explaining why compliance with each such paragraph is not feasible or is contrary to the best interests of the individuals who may receive the investigational new drug;

(*2*) Provides a written statement from an authorized official of the importing country's government. The statement must attest that the official agrees with the exporter's statement made under paragraph (b)(5)(i)(A)(*1*) of this section; explain that the drug is to be stockpiled solely for use of the importing country in a national emergency; and describe the potential national emergency that warrants exportation of the investigational new drug under this provision; and

(*3*) Provides a written statement showing that the Secretary of Health and Human Services (the Secretary), or his or her designee, agrees with the findings of the authorized official of the importing country's government. Persons who wish to obtain a written statement from the Secretary should direct their requests to Secretary's Operations Center, Office of Emergency Operations and Security Programs, Office of Public Health Emergency Preparedness, Office of the Secretary, Department of Health and Human Services, 200 Independence Ave. SW., Washington, DC 20201. Requests may be also be sent by FAX: 202–619–7870 or by e-mail: *HHS.SOC@hhs.gov*.

(B) Exportation may not proceed until FDA has authorized exportation of the investigational new drug. FDA may deny authorization if the statements provided under paragraphs (b)(5)(i)(A)(*1*) or (b)(5)(i)(A)(*2*) of this section are inadequate or if exportation is contrary to public health.

(ii) *Situations where the investigational new drug is to be used for a sudden and immediate national emergency.* There may be instances where exportation of an investigational new drug is needed so that the drug may be used in a sudden and immediate national emergency that has developed or is developing. In such cases:

(A) A person may export an investigational new drug under paragraph (b)(4) of this section without making an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(v), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), (b)(4)(ix), and/or (b)(4)(xi), provided that he or she:

(*1*) Provides a written statement explaining why compliance with each such paragraph is not feasible or is contrary to the best interests of the individuals who are expected to receive the investigational new drug and

(*2*) Provides sufficient information from an authorized official of the importing country's government to enable the Secretary, or his or her

designee, to decide whether a national emergency has developed or is developing in the importing country, whether the investigational new drug will be used solely for that national emergency, and whether prompt exportation of the investigational new drug is necessary. Persons who wish to obtain a determination from the Secretary should direct their requests to Secretary's Operations Center, Office of Emergency Operations and Security Programs, Office of Public Health Emergency Preparedness, Office of the Secretary, Department of Health and Human Services, 200 Independence Ave. SW., Washington, DC 20201. Requests may be also be sent by FAX: 202–619–7870 or by e-mail: *HHS.SOC@hhs.gov*.

(B) Exportation may proceed without prior FDA authorization.

(c) *Limitations*. Exportation under paragraph (b) of this section may not occur if:

(1) For drugs exported under paragraph (b)(1) of this section, the IND pertaining to the clinical investigation is no longer in effect;

(2) For drugs exported under paragraph (b)(2) of this section, the requirements in section 802(b)(1), (f), or (g) of the act are no longer met;

(3) For drugs exported under paragraph (b)(3) of this section, the requirements in section 802(c), (f), or (g) of the act are no longer met;

(4) For drugs exported under paragraph (b)(4) of this section, the conditions underlying the certification or the statements submitted under paragraph (b)(5) of this section are no longer met; or

(5) For any investigational new drugs under this section, the drug no longer complies with the laws of the importing country.

(d) *Insulin and antibiotics*. New insulin and antibiotic drug products may be exported for investigational use in accordance with section 801(e)(1) of the act without complying with this section.

Dated: November 16, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 05–23120 Filed 11–22–05; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Part 165

[COTP Jacksonville 05–154]

RIN 1625–AA87

Security Zone; St. John's River, Jacksonville, FL to Ribault Bay

AGENCY: Coast Guard, DHS.

ACTION: Temporary final rule.

SUMMARY: The Coast Guard is establishing a temporary moving security zone around foreign naval submarines in transit within the area between 12 nautical miles seaward from the baseline at the mouth of the St. John's River to Ribault Bay. The security zone includes all waters within 500 yards in any direction of the submarine. This rule prohibits entry into the security zone without the permission of the Captain of the Port (COTP) Jacksonville or his designated representative. Persons or vessels that receive permission to enter the security zone must proceed at a minimum safe speed, must comply with all orders issued by the COTP or his designated representative, and must not proceed any closer than 100 yards, in any direction, to the submarine. This security zone is needed to ensure public safety and to prevent sabotage or terrorist acts against the submarine.

DATES: This rule is effective from 8 a.m. on November 9, 2005, until 11:59 p.m. on December 1, 2005.

ADDRESSES: Documents mentioned in this preamble as being available in the docket are part of docket [COTP Jacksonville 05–154] and are available for inspection and copying at Coast Guard Sector Jacksonville Prevention Department, 7820 Arlington Expressway, Suite 400, Jacksonville, Florida 32211, between 8 a.m. and 4 p.m., Monday through Friday, except Federal holidays.

FOR FURTHER INFORMATION CONTACT: Ensign Kira Peterson at Coast Guard Sector Jacksonville Prevention Department, Florida telephone: (904) 232–2640, ext. 108.

SUPPLEMENTARY INFORMATION:

Regulatory Information

We did not publish a notice of proposed rulemaking (NPRM) for this regulation. Under 5 U.S.C. 553(b)(B), the Coast Guard finds that good cause exists for not publishing a NRPM. Publishing a NPRM, which would incorporate a comment period before a final rule could be issued, and delay the rule's effective date, is contrary to the public interest because immediate action is necessary to protect the public and waters of the United States.

For the same reasons, under 5 U.S.C. 553(d)(3), the Coast Guard finds that good cause exists for making this rule effective less than 30 days after publication in the **Federal Register**. The Coast Guard will issue a broadcast notice to mariners and will place Coast Guard vessels in the vicinity of this zone to advise mariners of the restrictions.

Background and Purpose

This rule is needed to protect foreign navy submarines from damage or injury from sabotage or other subversive acts, accidents or other causes of a similar nature, or to secure the observance of rights and obligations of the United States. Although this rule is effective from 8 a.m. on November 9, 2005, until 11:59 p.m. on December 1, 2005, the Coast Guard will only enforce this rule when a foreign navy submarine is transiting within the area between 12 nautical miles seaward from the baseline at the mouth of the St. John's River to Ribault Bay. Anchoring, mooring, or transiting within this zone is prohibited, unless authorized by the Captain of the Port, Jacksonville, Florida, or his designated representative. The temporary security zone encompasses all waters within 500 yards around the foreign naval submarine. Vessels or persons authorized to enter the zone must proceed at a minimum safe speed, must comply with all orders issued by the COTP or his designated representative, and must not proceed any closer than 100 yards, in any direction, to the submarine.

Regulatory Evaluation

This regulation is not a significant regulatory action under section 3(f) of Executive Order 12866, Regulatory Planning and Review, and does not require an assessment of potential cost and benefits under section 6(a)(3) of that Order. The Office of Management and Budget has not reviewed it under the order. It is not ''significant'' under the regulatory policies and procedures of the Department of Homeland Security (DHS) because these regulations will only be in effect for a short period of time and the impact on routine navigation is expected to be minimal.

Small Entities

Under the Regulatory Flexibility Act (5 U.S.C. 601–612), we considered whether this rule would have a