



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 1 and 251

[Docket No. FDA-2019-N-5711]

[RIN 0910-AI45]

Importation of Prescription Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to amend its regulations to implement a provision of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to allow importation of certain prescription drugs from Canada. If the rule is finalized as proposed, States or certain other non-federal governmental entities would be able to submit importation program proposals to FDA for review and authorization. An importation program could be co-sponsored by a pharmacist, a wholesaler, or another State or non-federal governmental entity. The rule, when finalized, would contain all requirements necessary for a State or other non-federal governmental entity and its co-sponsors, if any, to demonstrate that their importation program will pose no additional risk to the public's health and safety. In addition, the proposed rule would require that the State or non-federal governmental entity and its co-sponsors, if any, explain why their program would be expected to result in a significant reduction in the cost of covered products to the American consumer.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 75 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Submit

comments on information collection issues under the Paperwork Reduction Act of 1995 (PRA) by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 75 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 75 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see “Written/Paper Submissions” and “Instructions”).

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2019-N-5711 for “Importation of Prescription Drugs.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out,

will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:

<https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Submit comments on information collection issues under the PRA to the Office of Management and Budget (OMB) in the following ways:

- Fax to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, Fax: 202-395-7285, or email to oir_submission@omb.eop.gov. All comments should be identified with the title, Section 804 Importation Program Proposals--21 CFR part 251.

FOR FURTHER INFORMATION CONTACT: Lyndsay Hennessey, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 301-796-7605. With regard to the information collection: Domini Bean,

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I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to amend its regulations to implement section 804(b) through (h) of the FD&C Act (21 U.S.C. 384(b) through (h)) to allow importation of certain prescription drugs shipped from Canada. The purpose of the proposed rule is to lower prices and reduce out of pocket costs for American patients.

B. Summary of the Major Provisions of the Proposed Rule

Under the proposed rule, section 804 of the FD&C Act would be implemented through time-limited Section 804 Importation Programs (SIPs), which would be authorized by FDA and managed by States or certain other non-federal governmental entities and by their co-sponsors, if any (SIP Sponsors). A SIP could be co-sponsored by a pharmacist, a wholesaler, or another State or non-federal governmental entity.

FDA proposes that a SIP Sponsor specify the eligible prescription drugs that would be included in the SIP. To be eligible under the proposed rule, a drug would need to be approved

by Health Canada's Health Products and Food Branch (HPFB) and, but for the fact it bears the HPFB-approved labeling when marketed in Canada, it would need to otherwise meet the conditions in an FDA-approved new drug application (NDA) or abbreviated new drug application (ANDA). Essentially, eligible prescription drugs are those that could be sold legally on either the Canadian market or the American market with appropriate labeling.

Under the proposed rule, the SIP Proposal would also need to identify the foreign seller in Canada that will purchase the eligible prescription drug directly from its manufacturer, and the importer in the United States that will buy the drug directly from the foreign seller. While the initial SIP Proposal would identify just one foreign seller and one importer, once the SIP can show that it has consistently imported eligible prescription drug(s) in accordance with section 804 and the rule, the SIP Sponsor would be able to submit a supplemental proposal to add additional foreign sellers or importers. The supply chain for each drug under a SIP would be limited to three entities, i.e. one manufacturer, one foreign seller, and one importer.

FDA proposes that the foreign seller be a party that is licensed by Health Canada as a wholesaler and registered with FDA as a foreign seller, and that the importer be a wholesaler or pharmacist licensed to operate in the United States. Both the foreign seller and the importer would be subject to the supply chain security requirements proposed in this rulemaking and under the FD&C Act. Among other things, the foreign seller would have to ensure that a section 804 serial identifier (SSI), which is an alphanumeric serial number unique to each package or homogeneous case, is affixed or imprinted to each package and homogenous case of the drugs, and the importer would have to ensure that a product identifier meeting the requirements of section 582 of the FD&C Act (21 U.S.C. 360eee-1) (i.e., a product identifier that includes a National Drug Code, unique alphanumeric serial number of up to 20 characters, lot number, and

expiration date, in both human- and machine-readable format) is affixed or imprinted to each package or homogenous case of the drugs. The importer would also have to maintain records linking the product identifier affixed or imprinted on a package or homogenous case to the SSI that the foreign seller assigned.

After FDA has authorized a SIP Proposal, the importer would submit a Pre-import Request to FDA at least 30 days prior to the scheduled date of arrival or entry for consumption of a shipment containing an eligible prescription drug covered by the SIP, whichever is earlier. Entry and arrival of a shipment containing an eligible prescription drug would be limited under the proposed rule to the U.S. Customs and Border Protection (CBP) port of entry authorized by FDA. The importer, or authorized customs broker, would be required to electronically file an entry for consumption in the Automated Commercial Environment (ACE) or other electronic data interchange system authorized by CBP for each eligible prescription drug imported or offered for import into the United States. These entries would be filed as formal entries. If an eligible prescription drug is imported or offered for import that does not comply with section 804 of the FD&C Act and the provisions of this proposed rule, that drug would be subject to refusal under section 801 of the FD&C Act (21 U.S.C. 381).

The importer would need to arrange for statutorily prescribed testing of the drug for authenticity, degradation, and other statutory testing requirements by a qualifying laboratory in the United States, if the manufacturer does not perform the testing required under section 804, and would also need to ensure that the drug complies with all labeling requirements under the FD&C Act. Section 804 of the FD&C Act requires that the mandatory testing either be performed by the manufacturer of an eligible prescription drug or, if such testing is performed by the importer, that the manufacturer supply the information the importer needs to authenticate the

drug and to confirm that its labeling complies with all labeling requirements under the FD&C Act. In the proposed rule, FDA specifies that this information includes, among other things, any relevant testing protocols that the manufacturer has developed.

Under the proposed rule, the importer can choose to admit the drug or drugs specified in the section 804 pre-import request to an authorized Foreign Trade Zone (FTZ) and then conduct the required testing and relabeling, or alternatively, the importer can make an entry for consumption and request to recondition the drug or drug(s), which would entail the required testing and relabeling. Under the proposed rule, the results of this testing would be reviewed and accepted by FDA and subsequently the drug would have to be relabeled with labeling that complies with all labeling requirements under the FD&C Act before the drug can be distributed in the United States.

Pursuant to section 804(c)(3) of the FD&C Act, the proposed rule also sets forth post-importation requirements. Each SIP Sponsor would be required to provide FDA with data and information about its SIP, including the SIP's cost savings to the American consumer. An importer would be required to submit adverse event, medication error, field alert, and other reports to a drug's manufacturer and to FDA. If FDA or any participant in a SIP determines that a recall is warranted, the SIP Sponsor would be responsible for effectuating the recall. The proposed rule would require that each SIP have a written recall plan that describes the procedures to perform a recall of the product and specifies who will be responsible for performing the procedures.

A SIP is eligible for extension by FDA before the end of its approval period. A SIP may also be terminated by FDA at any time for the reasons outlined in this proposed rule.

C. Legal Authority

Section 804(l)(1) of the FD&C Act provides that section 804 shall become effective only if the Secretary certifies to the Congress that the implementation of this section will- pose no additional risk to the public's health and safety, and result in a significant reduction in the cost of covered products to the American consumer. The Secretary of the Department of Health and Human Services (the Secretary or the Secretary of HHS) would make this certification to Congress upon issuance of a final rule based on this proposal. FDA is also issuing this proposed rule under FDA's rulemaking authority regarding importation of prescription drugs under section 804(b) through (h) of the FD&C Act. The proposed rule is also being issued pursuant to FDA's authorities related to adulterated and misbranded drugs under sections 501 and 502 of the FD&C Act (21 U.S.C. 351 and 352); FDA's authorities with regard to wholesale distribution under section 503(e) of the FD&C Act (21 U.S.C. 353(e)); FDA's authority related to new drugs under section 505 of the FD&C Act (21 U.S.C. 355); as well as FDA's rulemaking, inspection, and importation authorities under sections 701(a), 704, and 801(a) of the FD&C Act, respectively (21 U.S.C. 371(a), 374, and 381).

D. Costs and Benefits

The proposed rule, if finalized, would allow commercial importation of certain prescription drugs from Canada through time-limited programs sponsored by at least one non-federal governmental entity with possible co-sponsorship by a wholesaler or pharmacist. As we lack information about the expected scale or scope of such programs, we are unable to estimate how they may affect U.S. markets for prescription drugs. In particular, we are unable to estimate the volume or value of drugs that may be imported under the SIPs or the savings to U.S. consumers who may participate in such programs.

Costs of the proposed rule may accrue to the Federal Government, SIP Sponsors, importers, and manufacturers of imported drugs. The Federal Government would incur one-time fixed costs to implement the rule as well as ongoing costs including those to review program proposals and periodic reports. SIP Sponsors would face costs to prepare SIP Proposals, implement approved SIPs, and produce SIP reports and records. If their drugs are imported into the United States from Canada, drug manufacturers may have to provide importers with certain information. These costs depend on the number and type of participating importation programs. We lack information to estimate these costs.

Finally, U.S. patients, as well as wholesale drug distributors, pharmacies, hospitals, and third-party payers, may all experience savings, but we lack information necessary to estimate such savings. As drug distributors realize savings in acquiring imported drugs and pass some of these savings to consumers and other parties in the drug supply chain, it is possible that U.S. drug manufacturers may experience a transfer in U.S. sales revenues to these parties.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
ACE	Automated Commercial Environment or any Other Electronic Data Interchange System authorized by the U.S. Customs and Border Protection
ANDA	Abbreviated New Drug Application
CBP	U.S. Customs and Border Protection
CGMP	Current Good Manufacturing Practice
COA	Certificate of Analysis
DIN	Drug Identification Number
DSCSA	Drug Supply Chain Security Act
FD&C Act	Federal Food, Drug, and Cosmetic Act
FTZ	Foreign Trade Zone
HPFB	Health Canada Health Products and Food Branch
NDA	New Drug Application
OMB	Office of Management and Budget
SIP	Section 804 Importation Program
SSI	Section 804 Serial Identifier

III. Background

Since 1938, the FD&C Act has required the submission of an application to FDA for a new drug before it is marketed in the United States. Under sections 301(d) and 505(a) of the FD&C Act (21 U.S.C. 331(d) and 355(a)), a new drug may not be introduced or delivered for introduction into interstate commerce, which includes importation into the United States, unless an application approved by FDA under section 505 is in effect for the drug. Unapproved new drugs include versions of FDA-approved drugs that are intended for sale outside of the United States, and which have not themselves been approved by FDA for marketing in the United States. (*United States v. Genendo Pharmaceutical, N.V.*, 485 F.3d 958 (7th Cir. 2007); *In Re Canadian Imp. Antitrust Litig.*, 470 F.3d 785, 789-90 (8th Cir. 2006).) Under section 801(a)(3) of the FD&C Act, FDA has authority to refuse admission of a drug that is offered for import if, among other things, it appears to be an unapproved new drug and, therefore, in violation of section 505 of the FD&C Act. Under section 801(d)(1)(A) of the FD&C Act, a prescription drug that is manufactured in a State and exported may only be imported into the United States by the manufacturer, except, in addition to another reason not relevant here, as provided in section 804. Under section 801(d)(1)(B) of the FD&C Act,¹ a prescription drug manufactured outside the United States may be imported into the United States for commercial use only in situations where the manufacturer has authorized the drug to be marketed in the United States and has caused the drug to be labeled to be marketed in the United States, except, in addition to another reason not relevant here, as provided in section 804.

¹ Elsewhere in this issue of the *Federal Register*, FDA is announcing the availability of a draft guidance that describes procedures to obtain an additional National Drug Code for an FDA-approved prescription drug that is imported into the United States in compliance with section 801 of the FD&C Act.

In 2000, Congress enacted legislation known as the Medicine Equity and Drug Safety (MEDS) Act as part of the Fiscal Year 2001 appropriations bill for the Department of Agriculture and related Agencies (Pub. L. 106-387). The MEDS Act added an earlier version of section 804 to the FD&C Act that, if implemented, would have allowed pharmacists or wholesalers in the United States to import certain prescription drugs without the authorization of the manufacturer. The MEDS Act was intended to “empower pharmacists and wholesalers to purchase FDA-approved medicines in Canada and pass the discounts along to American patients[.]” (146 Cong. Rec. S3692, 3693 (daily ed. May 9, 2000)).² The law required that, prior to implementation, the Secretary of HHS demonstrate that the importation of these drugs would pose no additional risk to the public’s health and safety and would result in a significant reduction in the cost of covered products to the American consumer. HHS was not able to make such demonstration (Ref. 1).

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) (Pub. L. 108-173) was signed into law on December 8, 2003. Section 1121 of the MMA amended section 804 of the FD&C Act to its current version, which, among other things, authorizes the Secretary of HHS, after consultation with the U.S. Trade Representative and the Commissioner of Customs, to issue regulations permitting pharmacists and wholesalers to import certain prescription drugs from Canada under certain conditions and limitations. For section 804 of the FD&C Act to become effective, the Secretary of HHS must certify that its implementation will “pose no additional risk to the public’s health and safety,” and that it will “result in a significant reduction in the cost of covered products to the American consumer.”

² While this statement seems to imply that these amendments were intended to only permit importation from Canada, the actual amendments contained no such restriction.

There has been interest for many years in allowing the importation of less expensive drugs from Canada to help American consumers benefit from these lower prices. However, no prior HHS Secretary has made the certification required under section 804(1) to begin implementing any part of section 804 of the FD&C Act. Past efforts have been unsuccessful in part because of concerns that: (1) FDA could not ensure the safety and effectiveness of drugs imported via such a program, (2) an importation program that opened the “closed” U.S. drug distribution system for prescription drugs could increase the opportunity for counterfeit and other substandard drugs to enter the supply chain, and (3) an importation program would not result in a significant reduction in costs to American consumers (Refs. 1 to 4).

In 2003, as part of the MMA, Congress directed HHS to conduct a study on the importation of prescription drugs. The results of this study were presented in a Task Force Report that was submitted to Congress in December 2004 (Ref. 5). The Task Force Report identified concerns about potential risks and challenges associated with implementing section 804, including, but not limited to:

- “The current system of drug regulation in the U.S. has been very effective in protecting public safety, but is facing new threats. It should be modified only with great care to ensure continued high standards of safety and effectiveness of the U.S. drug supply.”
- “Overall national savings from legalized commercial importation will likely be a small percentage of total drug spending and developing and implementing such a program would incur significant costs and require significant additional authorities.”
- “The public expectation that most imported drugs are less expensive than American drugs is not generally true. Generic drugs account for most prescription drugs used in the U.S. and are usually less expensive in the U.S. than abroad.”

- “The effects of legalized importation on intellectual property rights are uncertain but likely to be significant... These effects could create additional disincentives to develop breakthrough medicines and further limit any potential savings that might have been realized.”
- “Legalized importation raises liability concerns for consumers, manufacturers, distributors, pharmacies, and other entities. Consumers harmed by imported drugs may not have legal recourse against foreign pharmacies, distributors, or other suppliers. Entities in the pharmaceutical supply chain may take actions to protect themselves from liability that could ultimately raise the cost of drugs” (Ref. 5).

The continued rise of prescription drug prices since the issuance of the 2004 Task Force Report has raised concerns among policymakers, healthcare professionals, and American consumers. According to a 2017 United States Government Accountability Office (GAO) report, “[t]he amount of money people spend on prescription drugs has nearly doubled since the 1990s” (Ref. 6). Additionally, the GAO found that “[i]n 2015, expenditures for prescription drugs sold through retail pharmacies were estimated to account for nearly 12 percent of total personal health care services spending in the United States, up from approximately 7 percent of such spending through the 1990s.” The HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE) estimates that the United States spent about \$457 billion on prescription drugs in 2015 (Ref. 7). In 2009, by comparison, prescription drug spending in the United States was \$354 billion. Prescription drug spending is projected to continue to rise faster than overall health spending (Ref. 7).

FDA is committed to expanding Americans’ access to high-quality, safe and effective, affordable medicines. Congress has given FDA, as part of the Agency’s mission to promote and

protect the public health, responsibility for implementing laws intended to strike a balance between encouraging and rewarding innovation in drug development and facilitating robust and timely market competition. The Agency takes seriously its responsibility to ensure that the medicines Americans use are safe and effective. FDA also recognizes that “[a]ccess to affordable prescription drugs, many of which are needed to treat life-threatening and serious conditions, is a daily concern and challenge for many Americans.” (Ref. 5)

Most Americans (79 percent) say the cost of prescription drugs is “unreasonable” (Ref. 8). Prohibitive costs can lead to medication nonadherence, which negatively impacts health outcomes and contributes to increased healthcare costs in the United States (Ref. 9). In a recent national poll, almost one-third (29 percent) of U.S. adults have reported “not taking their medicines as prescribed” due to the expense, and almost 1 in 10 (8 percent) said this led to a decline in their condition (Ref. 8). National news outlets have reported on the dire consequences of patients rationing immunosuppressive medications needed after organ transplants or delaying cancer treatments because of costs (Refs. 10 and 11).

Contributing to public frustration on this issue is the disparity between prices that Americans pay for brand name medications as compared with other developed countries. The reasons for such price disparities are varied. Brand name prescription drugs (as distinct from generic drugs) often are more expensive in the United States than they are in other developed markets (Refs. 12 to 14). For instance, in 2017, Canada’s Patented Medicine Prices Review Board (PMPRB) found that patented medicines (i.e., drug products to which patents apply) cost on average three times more in the United States than Canada (Refs. 15 and 16). As a result of these price differentials, some American consumers have sought to import drugs from other countries in an effort to obtain treatments that may be otherwise inaccessible to them because of

cost. According to a national poll, millions of Americans have purchased prescription drugs from other countries (Refs. 17 and 18).

FDA has revisited the question of whether section 804 of the FD&C Act could be implemented so that the Secretary could make the required certification under section 804(l)(1). Past analyses regarding the feasibility of implementing section 804 did not consider the possibility of implementing section 804(b) through (h) of the FD&C Act solely through programs proposed by States or certain other non-federal governmental entities and their co-sponsors, if any, and authorized by FDA, as described in this proposed rule. FDA has reviewed these past analyses and proposes that while the concerns about public health and safety and the ability to achieve cost savings remain valid, section 804 of the FD&C Act can be implemented in a manner consistent with the certification criteria through programs, overseen by States or certain other non-federal governmental entities and their co-sponsors, if any, that require authorization by and reporting to FDA. These programs would be required to demonstrate to FDA that they could import drugs from Canada at no additional risk to the public's health and safety consistent with the requirements in section 804 of the FD&C Act and this proposed rule. These include, among other requirements, requirements relating to the types of drugs eligible for importation, the distribution channels and methods used for product traceability, and the testing of eligible prescription drugs for authenticity and degradation. In addition, in accordance with section 804, the proposed rule would require that drugs imported under section 804 meet the specifications of an FDA-approved NDA or ANDA. These programs would also be expected to demonstrate significant cost reductions to the American consumer. Merely because an importation purports to be done pursuant to section 804, that does not mean it has been authorized under section 804 and is compliant with section 804 of the FD&C Act and this rule, if finalized.

FDA is not proposing to implement the personal importation provisions in section 804(j) through this rulemaking. The internet provides consumers with instant access to information and services, including prescription medications. Medications that are purchased online and imported through international mail, express couriers, and other means pose significant challenges for FDA and its ability to adequately safeguard the quality and safety of drugs taken by U.S. consumers. While there are pharmacy websites that operate legally and offer convenience, privacy, and safeguards for purchasing medicines, there are many rogue online pharmacies that sell medicines at deeply discounted prices, often without requiring a prescription or adhering to other safeguards followed by pharmacies licensed by a State in the United States. These rogue online pharmacies are often run by sophisticated criminal networks that knowingly and unlawfully cause the importation of adulterated, counterfeit, misbranded and unapproved drugs into the United States. These criminals frequently use sophisticated technologies and are backed by larger enterprises intent on profiting from illegal drugs at the expense of American patients (Refs. 19 and 20). Consumers go to these websites believing they are buying safe and effective medications, but often they are being deceived and put at risk by individuals who put financial gain above patient safety.

For example, Canada Drugs Ltd. (“Canada Drugs”) was an internet-based pharmacy corporation located in Winnipeg, Manitoba, Canada, which purchased drugs from questionable sources that were outside FDA’s closed supply chain (Refs. 21 and 22). Canada Drugs and its subsidiaries put the public health at risk through widespread sales of misbranded and unapproved drugs to U.S. consumers at discounted prices (Ref. 23). Moreover, in two instances, Canada Drugs, through a subsidiary, distributed counterfeit versions of the cancer drugs Avastin and Altuzan (the Turkish version of Avastin) to healthcare providers in the United States. The

counterfeits contained no active ingredient. After Canada Drugs became aware that they had shipped counterfeit Avastin and Altuzan to medical clinics in the United States, they tried to conceal the problem. Canada Drugs never notified FDA or other U.S. authorities that it had shipped counterfeit cancer drugs containing no active ingredient to the United States (Ref. 22).

Further, drugs promoted as being from Canada or approved by Health Canada's HPFB that are offered to U.S. citizens in many instances are not actually from Canada and not approved by HPFB. Instead, these drugs are obtained from ever-evolving illicit sources of supply. A 2005 FDA analysis of drugs imported through International Mail Facilities revealed that while nearly half of imported drugs claimed to be Canadian or from Canadian pharmacies, 85 percent of those drugs originated elsewhere and were fraudulently represented as Canadian (Refs. 24 and 25). Typically, these products are smuggled into the United States after being transshipped to third party countries, such as Canada, in an effort to avoid detection and create a more trustworthy appearance (Ref. 25). Given these risks, and other concerns discussed in the Task Force Report (Ref. 5), the proposed rule, if finalized, would not implement personal importation provisions under section 804(j) of the FD&C Act.

In the intervening years since the Task Force Report was issued in 2004, Canada has amended its regulations to strengthen its oversight of both pharmaceutical manufacturing practices (Ref. 26) and pharmaceutical supply chain participants (Ref. 27). Regulatory harmonization between Canada and the United States has also increased bilaterally through the U.S.-Canada Regulatory Cooperation Council and through international organizations such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Pharmaceutical Inspection Co-operation Scheme initiatives, of which both FDA and Health Canada are members. In August 2019, FDA and Health Canada

announced a series of joint meetings in advance of each bi-annual ICH face-to-face meeting to seek the public's input on areas where harmonized ICH guidelines would be beneficial (Ref. 28).

Additionally, since the 2004 HHS Task Force report and efforts by Vermont and other States to implement importation programs in the early 2000s, pharmaceutical supply chains have continued to mature and consolidate, and the ability of companies engaged in the transaction of drugs to conduct business internationally and trace their products has strengthened. This maturation has further grown since 2013, following and due in part to the enactment of the Drug Supply Chain Security Act (DSCSA) (Title II of Pub. L. 113-54). Among other requirements, the DSCSA outlines steps to build an electronic, interoperable system to identify, trace, and verify certain prescription drugs as they are distributed among pharmaceutical supply chain trading partners.

As wholesale drug distributors and pharmacists actively participate, along with manufacturers and other trading partners, in the development of an interoperable electronic system by 2023 in accordance with standards established by FDA, as required under DSCSA, they have developed processes and methods for complying with requirements in place since 2015 for exchanging transaction information and verifying products. Industry stakeholders have steadily marched toward these goals (Ref. 29). With the implementation of the DSCSA, supply chain security is maturing due in part to these technological solutions adopted by manufacturers, wholesale distributors, pharmacists, and other trading partners that serve as important links to help protect U.S. consumers from illegitimate products. In addition, under the DSCSA, FDA, along with the States, exercises oversight over wholesale drug distributors and pharmacists, in addition to manufacturers.

To address the substantial public health risks associated with counterfeits of their prescription drugs, manufacturers around the world now use a number of technologies to detect whether a certain drug is legitimate or fake. These technologies include both overt and covert security technology to enable identification of their authentic drug. Technological advancements that support verification of these overt and covert security features have enhanced the ability to detect counterfeits at the border and prevent their introduction into U.S. commerce.

Finally, FDA believes that at this time it can implement section 804(b) through (h) of the FD&C Act because it proposes to do so through SIPs, which would be authorized by FDA and managed by States or certain other governmental entities and their co-sponsors, if any, and which would last for 2 years from the time a program imports its first eligible prescription drug, with the possibility of extensions for 2-year periods. A State or other governmental entity and its co-sponsors, if any, would need to demonstrate to FDA that, in accordance with the requirements proposed here, the importation would pose no additional risk to the public's health and safety and would be expected to result in a significant reduction in the cost of covered products to the American consumer.

IV. Legal Authority

Section 804(l)(1) of the FD&C Act provides that section 804 shall become effective only if the Secretary certifies to the Congress that the implementation of this section will pose no additional risk to the public's health and safety, and result in a significant reduction in the cost of covered products to the American consumer. The Secretary would make this certification to Congress upon issuance of a final rule based on this proposal. FDA is also issuing this proposed rule under FDA's rulemaking authority regarding importation of prescription drugs under section 804(b) through (h) of the FD&C Act. The proposed rule is also being issued pursuant to

FDA's authorities related to adulterated and misbranded drugs under sections 501 and 502 of the FD&C Act; FDA's authorities with regard to wholesale distribution under section 503(e) of the FD&C Act; FDA's authority related to new drugs under section 505 of the FD&C Act; as well as FDA's rulemaking, inspection, and importation authorities under sections 701(a), 704, and 801(a) of the FD&C Act.

V. Description of the Proposed Rule

FDA is proposing to establish new part 251 of Title 21 of the Code of Federal Regulations (CFR) to implement section 804(b) through (h) of the FD&C Act to allow importation of certain prescription drugs from Canada. FDA proposes to implement section 804 through time-limited SIPs, which would be authorized by FDA in 2-year increments and managed by SIP Sponsors, with the possibility of extensions for 2-year periods. If the rule is finalized as proposed, SIP Sponsors that want to facilitate the importation of certain drugs from Canada would be able to submit a SIP Proposal to FDA for review and authorization, in FDA's discretion.

We propose that every SIP be sponsored by a State, tribal, or territorial governmental entity. Under the proposed rule, a SIP could be co-sponsored by a pharmacist, wholesaler, or another State or other non-federal governmental entity. Co-sponsorship could introduce valuable flexibility (for example, multiple States could co-sponsor a plan with a large wholesaler) and allow SIPs to benefit from the experience of pharmacists and wholesalers, while preserving the advantages that accrue from sponsorship by at least one State or other governmental entity. We seek comments on this approach. We are specifically interested in receiving comments on what the division of responsibility between co-sponsors should be and whether there are certain arrangements that should not be permitted. For example, we seek comment on whether a

pharmacist or wholesaler should be able to be both a SIP co-sponsor and an Importer within the same SIP. If yes, we seek comment on what safeguards a SIP could include to provide for sufficient oversight of a co-sponsor that is also acting as the Importer of the SIP. We also seek comment on whether non-governmental entities other than pharmacists and wholesalers, such as group purchasing organizations, pharmacy benefit managers, or union health and welfare benefit plans, should be permitted to co-sponsor SIPs.

This notice of proposed rulemaking (NPRM) is not intended to address the applicability of the Medicaid drug rebate program for drugs under a SIP, which may be addressed in further guidance or rulemaking from HHS as appropriate.

We considered whether to allow pharmacists or wholesalers to be SIP Sponsors without a State, tribal, or territorial governmental entity as a co-sponsor. We believe that a State, tribal, or territorial governmental entity should oversee each SIP because only a State, tribal, or territorial government entity would be in a position to demonstrate that it licenses or regulates pharmacists, wholesalers, and others in the prescription drug supply chain. For example, States provide the primary oversight of wholesale distributors' storage, handling, and distribution practices to ensure the quality of drugs is maintained. States also ensure that pharmacies and pharmacists comply with statutes and regulations governing the practice of pharmacy, which includes dispensing of drugs to patients. States have the authority to inspect pharmaceutical supply chain participants and to take disciplinary action against them if warranted. States also have tools that they can use to respond rapidly should activities under their SIP adversely affect the public health. We conclude that a plan that has at least one sponsor that is a State, tribal, or territorial governmental entity under which pharmacists or wholesalers import drugs would offer enhanced accountability and protect the public health.

Although this NPRM proposes to require at least one SIP Sponsor that is a State, tribal, or territorial government for each SIP, we seek comment on whether it could be possible for a pharmacist or wholesaler to be a SIP Sponsor without a State, tribal, or territorial government co-sponsor, while posing no additional risk to the public's health and safety. Although we cannot foresee at this time how this approach could be adopted without posing additional risk to the public's health and safety, if we receive information that demonstrates how a proposal that does not include a State, tribal, or territorial government co-sponsor would provide the same level of assurance of safety as a proposal with such a co-sponsor, we would consider having the final rule account for this possibility. Accordingly, we have provided a proposed alternative codified provision for comment that would also allow pharmacists or wholesalers to sponsor a SIP without a co-sponsor. This alternative codified provision appears under "Option 2" in proposed § 251.2. If we do not receive comments containing adequate information for FDA to justify such an allowance, we intend to omit the "Option 2" provision when we finalize this rule. In addition, as with any other proposed codified provision, if we decide to provide for additional types of Sponsors, the proposed codified provision under "Option 2" may be modified when this rule is finalized. In addition, among other potential revisions that may be necessary, if the final rule were to permit a pharmacist or wholesaler to be a SIP Sponsor without a State, tribal, or territorial government co-sponsor, we would include in the final rule those additional safeguards that would be applicable to most, and perhaps all, proposals without a State, tribal, or territorial government co-sponsor.

A SIP Sponsor could also be defined to include additional or different categories of sponsors and/or to exclude the possibility of co-sponsors where the SIP Sponsor is not a State, tribal, or territorial governmental entity. A co-sponsor could also be defined to include

additional or different categories of co-sponsors. Additionally, we seek comment on what safeguards a SIP would need to include to provide for sufficient oversight of a SIP Sponsor who is also acting as the Importer for the SIP.

In its SIP Proposal, the SIP Sponsor would need to show, in accordance with the requirements proposed in this rule, that its proposed importation will pose no additional risk to the public's health and safety. A SIP Proposal would also need to explain why the Sponsor expects the proposal would result in a significant reduction in the cost to the American consumer of the prescription drugs that the Sponsor seeks to import. The explanation regarding the significant reduction in the cost of covered products to the American consumer would need to include any assumptions and uncertainty, and it would need to be sufficiently detailed that it can be evaluated by another component of HHS, as directed by the Secretary, which would make a recommendation to FDA.

Where a SIP Proposal meets the requirements of section 804(b) through (h) of the FD&C Act and this proposed rule, FDA may nonetheless decide, in its discretion, not to authorize the SIP Proposal. Among other reasons, FDA may decide not to authorize a SIP Proposal because of potential safety concerns with the program, because of the relative likelihood the program would not result in significant enough cost savings (based on the recommendation of another HHS component as directed by the Secretary), because FDA needs to limit the number of authorized programs to effectively and efficiently monitor the program, or in light of other resource demands.

In its SIP Proposal, a State or other non-federal governmental entity and its co-sponsors, if any, would specify the eligible prescription drugs it seeks to import. To be eligible, a drug would need to be approved by Canada's HPFB and, but for the fact it bears the HPFB-approved

labeling, it would need to meet the conditions in an FDA-approved NDA or ANDA. The SIP Proposal would also need to identify the Foreign Seller in Canada that would purchase the drug directly from its manufacturer, and the Importer in the United States that would buy the drug directly from the Foreign Seller. FDA proposes that the Foreign Seller be registered with FDA as a Foreign Seller and be licensed by Health Canada as a wholesaler, and that the Importer be a wholesaler or pharmacist licensed in the United States.

Due to resource constraints that limit FDA's ability to provide effective safety oversight, we considered placing a limit on the number of SIP Proposals that FDA would authorize and the number of SIPs that FDA would oversee. We considered limiting each State, tribal, or territorial governmental entity and its co-sponsors, if any, to submitting one SIP Proposal for one supply chain. However, there may be State, tribal, or territorial governmental entities and their co-sponsors, if any, that wish to use more than one Foreign Seller or more than one Importer. Other State, tribal, or territorial governmental entities may not wish to submit a SIP Proposal. For this reason, we do not propose to perpetually limit the total number of Foreign Sellers or Importers with which a SIP Sponsor can work, although we do note that each Foreign Seller must buy the drugs to be imported directly from the manufacturer and sell those drugs directly to the Importer. After a State, tribal, or territorial governmental entity and its co-sponsors, if any, has an authorized SIP that has consistently imported eligible prescription drugs in accordance with section 804 of the FD&C Act and this rule, that State, tribal, or territorial governmental entity and its co-sponsors, if any, would be able to submit a supplement to the SIP Proposal to add a Foreign Seller or Importer. We do not expect to be able to find that a SIP Sponsor has consistently imported drugs in accordance with section 804 of the FD&C Act and this rule before it submits its first quarterly report to FDA.

After FDA has authorized a SIP Proposal, the Importer would submit a request to FDA at least 30 days prior to the scheduled date of arrival or entry for consumption of a shipment containing an eligible prescription drug, whichever is earlier. Entry and arrival of a shipment containing an eligible prescription drug would be limited under the proposed rule to the CBP port of entry authorized by FDA. The Importer would be required to electronically file an entry for consumption, including the data elements that FDA requires, in ACE or other electronic data interchange system authorized by CBP for each eligible prescription drug imported or offered for import into the United States. These entries would be filed as formal entries. If an eligible prescription drug is imported or offered for import that does not comply with section 804 or the provisions of this proposed rule, that drug would be subject to refusal under section 801 of the FD&C Act.

In accordance with section 804(e)(1) of the FD&C Act, the proposed rule would require the manufacturer or the Importer to conduct testing of the drugs to be imported for authenticity, degradation, and “to ensure that the prescription drug is in compliance with established specifications and standards” (Statutory Testing). Also, in accordance with section 804(e)(1), the proposed rule would require that the Statutory Testing be done at a qualifying laboratory in the United States. The Importer would also have to ensure that the drug bears the required U.S. labeling.

Under section 804(e)(2) of the FD&C Act, if the manufacturer of an eligible prescription drug does not test the drug itself, the testing would need to be performed by the Importer using information supplied by the manufacturer, including all the information needed to authenticate the drug and confirm that its labeling complies with labeling requirements under the FD&C Act. In the proposed rule, FDA specifies that this information includes, among other things, any

testing methodologies and protocols that the manufacturer has developed that the Importer needs to conduct the Statutory Testing.

Under the proposed rule, the Importer can choose to admit the drug or drugs specified in the section 804 Pre-Import Request to an authorized FTZ and then conduct the required testing and relabeling or, alternatively, the Importer, or an authorized customs broker, can make an entry for consumption and request to recondition the drug or drugs, which would entail the required testing and relabeling. Under the proposed rule, the results of the Statutory Testing would need to be reviewed and found acceptable by FDA, and the drug would have to bear the required U.S. labeling, before the drug is sold in the United States.

Both the Foreign Seller and the Importer would be subject to the supply chain security requirements proposed in this rule. Among other things, the Foreign Seller would have to ensure that the product is serialized at the package level and adhere to applicable DSCSA obligations. The Importer would have to ensure that a product identifier meeting the requirements of section 582 of the FD&C Act is affixed or imprinted to each package and homogenous case of the drugs and adhere to other existing DSCSA obligations, as described below.

The proposed rule also sets forth post-importation requirements. Each SIP Sponsor would be required to provide FDA with data and information about its SIP, including the SIP's cost savings to the American consumer. An Importer would be required to submit adverse event, medication error, field alert, and other reports to a drug's manufacturer and to FDA. If FDA or any participant in a SIP determines that a recall is warranted, the SIP Sponsor would be responsible for effectuating the recall. The proposed rule would require that SIPs have a written recall plan that describes the procedures to perform a recall of the product and specifies who will be responsible for performing the procedures.

Once effective, section 804(b) of the FD&C Act directs the Secretary, after consultation with the U.S. Trade Representative and the Commissioner of Customs, to promulgate regulations permitting pharmacists and wholesalers to import prescription drugs from Canada into the United States. Section 804(c) specifies that the regulations shall require that safeguards be in place to ensure that each prescription drug imported under the regulations complies with section 505 of the FD&C Act (including with respect to being safe and effective for the intended use of the prescription drug), with section 501 of the FD&C Act (relating to adulteration), with section 502 of the FD&C Act (relating to labeling and misbranding) and with other applicable requirements of the FD&C Act. The statute also provides that the regulations require that Importers comply with section 804(d)(1) of the FD&C Act, under which an Importer of a prescription drug under 804(b) must submit certain information and documentation relating to the drug to the Secretary. In addition, the regulations must require compliance with section 804(e), which requires that importers or manufacturers test drugs imported under section 804 at a qualifying laboratory.

Eligible prescription drugs must be in compliance with section 804 of the FD&C Act and with other applicable requirements of the FD&C Act, including sections 505 (including with respect to being safe and effective for the intended use of the prescription drug), 502, and 501 of the FD&C Act, in order to be imported. This proposed regulation would create new exemptions from the statutory requirement of adequate directions for use under section 502(f)(1) of the FD&C Act and from certain requirements in section 582 of the FD&C Act. Section 804(c)(3) of the FD&C Act provides the Secretary the authority to add regulatory requirements, as appropriate, as a safeguard to protect the public health or to facilitate the importation of prescription drugs. Under the authority of section 804(c) of the FD&C Act, we are proposing

additional provisions that we have determined to be appropriate as a safeguard to protect the public health or as a means to facilitate the importation of eligible prescription drugs.

Section 804(l)(1) of the FD&C Act provides that section 804 shall become effective only if the Secretary certifies to the Congress that the implementation of this section will pose no additional risk to the public's health and safety, and result in a significant reduction in the cost of covered products to the American consumer. After consideration of comments received on this NPRM, if warranted, the Secretary will make this certification to Congress concurrent with finalization of this rule. The Secretary's certification will be conditioned on each authorized SIP meeting the relevant requirements of section 804 of the FD&C Act and this rule, including the use of time-limited importation programs as described in this document. If one or more of the provisions in this rule becomes invalid, in addition to the entire rule becoming invalid, the certification would become null and void because the certification is based on a finding that implementation of section 804 will pose no additional risk to the public's health and safety, and that finding would no longer be accurate because it would have been based on a final rule that contains all the requirements that were included when published. We are not implementing section 804(j) of the FD&C Act relating to importation by individuals at this time.

A. Scope/Applicability

These proposed amendments to the regulations at part 251 would apply to eligible prescription drugs that are imported from Canada into the United States pursuant to an importation program authorized by FDA under section 804 of the FD&C Act.

B. Definitions

The proposed rule contains a number of definitions for terms used in the rule. Some of these definitions are provided in section 804 of the FD&C Act or cross-reference definitions elsewhere in part 251. We seek comment on our proposed definitions.

Subject to certain exclusions, section 804(a)(3) defines a “prescription drug” as a drug subject to section 503(b) of the FD&C Act, which is the provision requiring a prescription for drugs that are not safe for use except under the supervision of a healthcare practitioner. For purposes of this regulation, we propose to define “eligible prescription drug” to mean a drug subject to section 503(b) of the FD&C Act that has a marketing authorization from HPFB and, but for the fact it bears the HPFB-approved labeling, also meets the conditions in an FDA-approved NDA or ANDA, including those relating to the drug substance, drug product, production process, quality controls, equipment, and facilities. Essentially, eligible prescription drugs are those that could be sold legally on either the Canadian market or the American market with appropriate labeling. An eligible prescription drug would need to be relabeled with the required U.S. labeling, including the carton and container labels, prescribing information, and any patient labeling, before it can be sold in the United States.

In addition, to be eligible for importation under section 804 of the FD&C Act, the proposed rule would require that a prescription drug be marketed in the United States currently. We believe that FDA will be better able to determine if there is a safety issue with an imported HPFB-approved drug if the FDA-approved drug is currently marketed, because that will make it more likely that there will be current adverse event reports, medication error reports, and product quality complaints about the FDA-approved drug. In addition, a comparison between the cost of the HPFB-approved drug sold in Canada and the cost of the FDA-approved drug sold in the

United States may be necessary to establish that importation has resulted in a significant reduction in the cost of covered products to the American consumer.

Section 804(a)(3) of the FD&C Act excludes several categories from the definition of prescription drug, including controlled substances, biological products, infused drugs (including a peritoneal dialysis solution), intravenously injected drugs, and drugs that are inhaled during surgery. The proposed regulation excludes these categories from the definition of “eligible prescription drug.” In addition, we propose to exclude drugs that are subject to risk evaluation and mitigation strategies (REMS). Section 505-1 of the FD&C Act, which authorizes FDA to require REMS, was passed after section 804 of the FD&C Act. REMS drugs are high-risk products with known safety issues. REMS programs are mandated by FDA but implemented by manufacturers. In order to implement and assess a REMS, a manufacturer needs to have control over the drug that is the subject of the REMS. For example, a REMS could require that a medication’s labeling include a Medication Guide for patients. The manufacturer would not be able to ensure that this is done for drugs imported under section 804 of the FD&C Act because these drugs are relabeled by the Importer. Similarly, if it is a requirement of a REMS that a manufacturer provide certain information about a drug to prescribers, this could be complicated by the presence in the supply chain of versions of that drug that are imported by SIPs and so have different NDC numbers. Finally, for REMS that require tight controls on distribution of the drug in order to mitigate risks, use of Foreign Sellers will make it much more difficult to maintain those restrictions and could introduce gaps that have a significant impact on the safety of the drug.

The proposed regulation also excludes drugs that do not meet the definition of a “product” for purposes of section 582 of the FD&C Act. The DSCSA, which added section 582,

was passed after section 804 of the FD&C Act. As explained earlier, one reason that FDA believes that at this time it can implement section 804(b) through (h) of the FD&C Act is the DSCSA's electronic, interoperable system to identify, trace, and verify certain prescription drugs as they are distributed among pharmaceutical supply chain trading partners. Drugs that are imported under section 804 of the FD&C Act must meet the definition of a DSCSA "product" so that they are subject to all DSCSA identification, tracing, and verification requirements.

Under the proposed rule, a SIP Sponsor would need to explain in its SIP Proposal how it will address any concerns arising from the manufacture, storage, and transport of each eligible prescription drug, including concerns related to controlling contamination, preserving sterility, and ensuring stability. We considered excluding other categories of products from eligibility for importation, including: (1) drug-device combination products that are approved under section 505 of the FD&C Act, whether all such products or certain specific ones, such as dry powder inhalers, metered-dose inhalers, and transdermal patch products; (2) inhaled drugs; (3) modified-release drugs; (4) sterile drugs; (5) ophthalmic drugs; (6) narrow therapeutic index drugs; (7) drugs with boxed warnings; and (8) drugs requiring special storage conditions. While each of these categories of products could pose potentially heightened safety concerns, we did not exclude these categories of products from eligibility in this proposed rule. Instead, we propose that FDA will determine whether a product that falls into one of these categories can be imported safely in the context of a specific SIP Proposal on a product-by-product basis. If the product to be imported is a combination product, this would include whether requirements specific to combination products would be met. We request comments on this approach.

The definition of "prescription drug" in section 804(a)(3) of the FD&C Act also excludes "a drug which is a parenteral drug, the importation of which...is determined by the Secretary to

pose a threat to the public health.” We note that several categories of parenteral drugs--infused drugs, intravenously injected drugs, and drugs that are inhaled during surgery--are specifically excluded from importation under section 804 of the FD&C Act. We propose to exclude two other categories of parenteral drugs, intrathecally injected drugs and intraocularly injected drugs, from the definition of eligible prescription drug. Intrathecal and intraocular injection pose potentially significant risks because these routes of administration bypass some of the body’s natural defenses. In fact, they pose more risks than intravenous injection, which is excluded by statute from importation under section 804 of the FD&C Act. We propose that other parenteral drugs that are not excluded from importation under section 804 of the FD&C Act or this proposed rule be evaluated in the same way as drugs with other routes of administration. An importation program that seeks to import any eligible prescription drug would have to demonstrate that it can do so without posing additional risk to the public’s health and safety.

Consistent with section 804(f) of the FD&C Act, we propose to define “Foreign Seller” to mean an establishment within Canada engaged in the distribution of an eligible prescription drug that is imported or offered for importation into the United States. As discussed later in this document, under the proposed rule, Foreign Sellers would be required to be licensed by Health Canada as drug wholesalers and be registered with a provincial pharmacy regulatory authority to distribute HPFB-approved drugs. Under the proposed rule, a Foreign Seller could not be licensed to distribute drugs that are approved by countries other than Canada and that are not HPFB-approved for distribution in Canada. A Foreign Seller also must be registered with FDA as required by section 804 of the FD&C Act.

We propose to define “Importer” to mean a U.S. distributor that is a State- or FDA-licensed wholesale drug distributor or a State-licensed pharmacist and that is the U.S. owner of an eligible prescription drug at the time of importation of the drug into the United States.

We propose to define “manufacturer” to include an applicant, as defined in 21 CFR 314.3, who owns an approved NDA or ANDA for an eligible prescription drug, or a person who owns or operates an establishment that manufactures an eligible prescription drug. Manufacturer also means a holder of a drug master file containing information necessary to authenticate an eligible prescription drug. These entities are those that would have the necessary information required of manufacturers in section 804 and the requirements proposed in this rule.

C. Section 804 Importation Program Proposals and Section 804 Pre-Import Requests

Subpart B of the proposed rule provides the procedures for the submission and evaluation of SIP Proposals for time-limited SIPs. Subpart B also covers the submission of Pre-Import Requests by the Importer, which would seek FDA’s permission to begin importation of a particular eligible prescription drug(s). In addition, Subpart B outlines the procedures FDA proposes to use to authorize, revise, revoke, and extend SIPs.

Under the proposed rule, once a SIP receives FDA authorization, the SIP’s Foreign Seller can purchase eligible prescription drugs with the intent to sell them to the SIP’s Importer for importation under section 804 of the FD&C Act, and the SIP’s Importer can seek FDA’s permission to start importation of the drugs by submitting a section 804 Pre-Import Request, as described later in this document. The Pre-Import Request would include, among other things, a detailed description of the plan for conducting the testing required under section 804 of the FD&C Act and an attestation from the manufacturer that, but for the fact that it bears the HPFB-

approved labeling, the HPFB-approved drug meets the conditions in the FDA-approved drug's NDA or ANDA.

Once FDA grants the section 804 Pre-Import Request, the Importer may start the process for the importation of an eligible prescription drug identified in the Pre-Import Request. The Agency's grant of the section 804 Pre-Import Request by itself does not confer any type of right to import. To be imported notwithstanding section 801(d)(1) of the FD&C Act, a particular importation would need to meet the requirements of section 804 and this regulation, including that the prescription drug comply with sections 501, 502, and 505 of the FD&C Act.

The Importer can choose to admit the drug(s) specified in the Section 804 Pre-Import Request to an authorized FTZ and then conduct the required testing and relabeling before offering the drug for entry. Alternatively, the Importer can make an entry and request, under section 801(b) of the FD&C Act and § 1.95 (21 CFR. 1.95), to recondition the drug(s), which would entail the required testing and relabeling. The results of the Statutory Testing would need to be reviewed and found acceptable by FDA before the drugs are relabeled and sold in the United States. We believe this is necessary to prevent having relabeled drugs refused entry and exported back to Canada where they may subsequently be sold illegally back into the United States or elsewhere.

1. The Section 804 Importation Program Proposal

The proposed regulations provide that a SIP Sponsor that seeks to implement a SIP to import prescription drugs from Canada would need to submit a proposal to FDA in electronic form to FDA's Electronic Submissions Gateway (ESG) or to an alternative transmission point identified by the Agency.

The proposal would need to include the following:

- A cover sheet with the name or names of the SIP Sponsor and co-sponsors, if any, and the name and contact information for the point of contact with FDA during its review of the proposal;
- A table of contents;
- An introductory statement that includes an overview of the SIP Sponsor's SIP Proposal; and
- The SIP Sponsor's importation plan.

The overview in the introductory statement would need to identify the State or a tribal or territorial governmental entity that is going to sponsor the SIP, along with any co-sponsors. The overview would also list each of the eligible prescription drugs that the SIP Sponsor seeks to import and provide the name and address of the manufacturer of the finished dosage form for each drug, as well as the name and address of the manufacturer of the active pharmaceutical ingredient (API), if that information is available to the SIP Sponsor. If the API information is not available to the SIP Sponsor at the time their proposal is submitted, the Importer would need to provide it later in the process, when it submits a Pre-Import Request.

The overview in the introductory statement would also need to provide the name and address of the Foreign Seller who will export the drug from Canada to the United States, as well as the name and address of the Importer in the United States. The overview would need to summarize how the SIP Sponsor will ensure (1) that the imported eligible prescription drugs meet the Statutory Testing requirements, (2) that the labeling requirements of the FD&C Act and this rule are met, (3) that the supply chain is secure, and (4) that the post-importation pharmacovigilance and other requirements of the FD&C Act and this rule are met. Finally, the

overview would need to summarize the proposer's reasons for expecting that the significant reduction in cost from the importation accrues to the American consumer.

Under the proposed rule, the content of a SIP Proposal would include the following. The SIP Proposal would need to identify the State or tribal or territorial governmental entity that is going to sponsor the SIP, along with its co-sponsors, if any. The SIP Proposal would also need to identify the licensed wholesale drug distributor or licensed pharmacist that will act as the Importer and explain its legal relationship to the SIP Sponsor. Only a pharmacist or wholesaler could import drugs under section 804 of the FD&C Act and this rule. The SIP Proposal would need to identify each of the other entities in the supply chain and explain their legal relationship to the SIP Sponsor, if any, including the finished dosage form manufacturer and the Foreign Seller. The SIP Proposal would need to state and provide supporting evidence to establish that the Importer and the Foreign Seller meet all the requirements in section 804 and this proposed regulation.

FDA proposes to require that a SIP Proposal include the Health Canada inspectional history for the previous 5 years, or if the Foreign Seller has been licensed for less than 5 years, for the duration of its period of licensure, and the State and Federal inspectional history for the Importer for the previous 5 years, or if the Foreign Seller has been licensed for less than 5 years, for the duration of its period of licensure. The SIP Sponsor would also need to provide an attestation containing a complete disclosure of any past or pending civil penalties or violation, or criminal convictions or violations, of applicable State, Federal, or Canadian laws regarding drugs or devices against the Foreign Seller or Importer or an affirmation and attestation that the Foreign Seller or Importer has not been involved in, or convicted of, any such criminal or prohibited acts. Such attestation would need to include principals, any shareholder who owns 10

percent or more of outstanding stock in any non-publicly held corporation, directors, officers, and any facility manager or designated representative of such manager. We also propose that the SIP Proposal include a list of all disciplinary actions, along with the date of and parties to any action, imposed against the Foreign Seller or the Importer by State, Federal, or Canadian regulatory bodies, including any such actions against the principals, owners, directors, officers, or any facility manager or designated representative of such manager over the previous 7 years. We seek comment on whether the rule should require additional or alternative background information and on whether the background information requirement should cover additional or alternative individuals or entities.

As part of demonstrating that the proposed importation will pose no additional risk to the public's health and safety, the SIP Proposal would need to set forth all the steps the SIP Sponsor would need to take to ensure that the supply chain is secure, including ensuring that the Foreign Seller is able to serialize the drugs to be imported with an SSI. The SIP Proposal would need to include the steps that the SIP Sponsor will take to ensure that the storage, handling, and distribution practices of supply chain participants, including transportation providers, maintain and ensure the quality and security of the drugs. The storage and handling conditions and practices must meet the minimum requirements of 21 CFR part 205. The SIP Proposal would also need to set forth the Importer's responsibility for screening the drug(s) that it imports for issues or problems, including whether they are adulterated, counterfeit, damaged, tampered with, or expired, and the Foreign Seller's and the Importer's responsibilities for adverse event, medication error, field alert reports, or other reporting, in addition to a detailed plan for effectuating any recalls. The SIP Sponsor would have to explain how it will obtain recall or market withdrawal information and how it will ensure that recall or market withdrawal

information is shared among the SIP Sponsor, the Foreign Seller, the Importer, and FDA and provided to the manufacturer.

The SIP Proposal would also need to identify the FDA-registered repackager or relabeler in the United States that will relabel the imported drugs with the required U.S. labeling, including the carton and container labels, prescribing information, and any patient labeling, such as medication guides, instruction for use documents, and patient package inserts. The proposed rule would also require that the SIP Proposal describe the ways in which the SIP Sponsor will educate pharmacists, healthcare providers, and patients about its SIP. We seek comment on whether a SIP Proposal should also be required to describe the SIP Sponsor's plan for ensuring that the FDA-approved patient labeling is dispensed to patients with the drug imported under section 804 of the FD&C Act. In its proposal, the SIP would need to provide supporting evidence to establish that the repackager or relabeler is registered with FDA, as required by section 510(b) of the FD&C Act (21 U.S.C. 360(b)) and in accordance with part 207 (21 CFR part 207), and that any objectionable conditions or practices identified during its most recent FDA inspection have been addressed satisfactorily. While an imported drug would need to be relabeled, it would need to remain in the manufacturer's original container-closure system and not be repackaged, except to the limited extent necessary to relabel it, as described in this proposed rule.

Under the proposed rule, the SIP Proposal would be required to identify each HPFB-approved prescription drug that the SIP Sponsor seeks to import. The SIP Proposal would also be required to include the proprietary and established names of the HPFB-approved product and of its FDA-approved counterpart and confirm that the FDA-approved drug is currently marketed. It would need to provide a description of all the information that is available about the HPFB-

approved product and its FDA-approved counterpart and would be required to include the name and quantity of the active pharmaceutical ingredient(s) of the two drug products, the inactive ingredients of the two products, and the dosage form of the two drug products. The proposal would also need to include the HPFB-approved product's drug identification number (DIN), and the FDA-approved product's National Drug Code (NDC) and NDA or ANDA numbers. The proposal would also need to include the HPFB-approved drug's labeling. Under the proposed rule, the proposal would be required to include the FDA-approved drug's labeling and the FDA-approved labeling with the revisions necessary for the HPFB-approved drug to meet the requirements of this rule, as well as a side-by-side analysis of the FDA-approved drug's labeling and the proposed labeling to help demonstrate that the applicable FDA labeling requirements and the requirements of this rule are met.

The proposed rule would also require that the proposal identify the establishment where the active ingredient for each drug is manufactured, if this information is available, and the establishment where the finished dosage form for each drug is manufactured, if this information is available. This information is important for FDA to adequately assess whether the eligible prescription drug meets the conditions in an approved NDA or ANDA. If this information is not available to the SIP Sponsor at the time that the proposal is submitted, it would need to be provided later by the Importer in the Pre-Import Request.

The Statutory Testing that would be done under the proposed rule should be described in as much detail as possible in the SIP Proposal. The proposal would also need to explain how the SIP Sponsor will ensure that any information that the manufacturer provides to the Importer to allow the Importer to conduct the Statutory Testing would be kept in strict confidence and used only for purposes of testing or otherwise complying with the FD&C Act, as required by section

804(e)(2)(B). The information that the manufacturer provides must not be disseminated except to the qualified laboratory that will test the drug and to FDA, and the SIP Sponsor would need to explain how it will ensure that the information is not disseminated to any person by the qualified laboratory. If confidential manufacturer information is disclosed beyond the parameters described above, FDA will terminate the SIP. Moreover, a violation of any of these regulations, including this provision, is a prohibited act under section 301(aa) of the FD&C Act. An Importer that fails to comply with the requirement that the manufacturer's information be kept in strict confidence and be used only for testing or otherwise complying with the FD&C Act can be imprisoned for not more than 10 years under section 303(b)(6) of the FD&C Act (21 U.S.C. 333(b)(6)), fined under 18 U.S.C. 3571, or both. We seek comments on this approach.

The proposal would also need to indicate which laboratory in the United States will conduct the testing described in section 804(d)(1)(J) and (L) of the FD&C Act, which is discussed later in this document, and it would need to establish that the laboratory is located in the United States and is qualified to conduct the tests. As discussed later in this document, we propose that when FDA authorizes a SIP Proposal, FDA would thereby approve the laboratory identified in the proposal as a "qualifying laboratory" for purposes of section 804, as required by section 804(a)(4) of the FD&C Act. To be approved as a qualifying laboratory, a laboratory would need to have ISO 17025 accreditation and comply with the applicable elements of the pharmaceutical current good manufacturing practice (CGMP) requirements in parts 210 and 211 (21 CFR parts 210 and 211). It would need to have an FDA inspection history and satisfactorily addressed any objectionable conditions or practices identified during its most recent FDA inspection.

We recognize that not all data and information needed to show that a HPFB-approved drug meets the conditions in an FDA-approved NDA or ANDA may be available to a SIP Sponsor at the time that it submits its SIP Proposal. For example, testing results would not be available until the Importer receives a shipment of an eligible prescription drug and conducts the Statutory Testing. FDA may authorize a SIP based on the available information about a drug. An Importer will not be able to sell a drug imported under section 804 of the FD&C Act in the United States until the testing described in section 804(d) is completed satisfactorily, and the Importer has secured the information from the manufacturer described in section 804(e) that is needed to show that the drug meets the conditions of an approved NDA or ANDA and poses no additional risks to the public's health and safety.

Finally, the SIP Proposal would need to explain how the SIP Sponsor expects that the SIP would result in a significant reduction in the cost to the American consumer of the prescription drugs that the SIP Sponsor seeks to import. The explanation would need to include any assumptions and uncertainty, and it would need to be sufficiently detailed to allow for a meaningful evaluation. We propose that whether a reduction in cost is significant be determined in the context of considering a specific proposal. We seek comment on the factors that should be considered in determining whether a reduction in the cost of covered products is significant.

To demonstrate expected cost savings, a SIP Sponsor could compare anticipated acquisition costs or consumer prices per unit of each drug that the SIP Sponsor is seeking to import. For example, a SIP Sponsor could compare the anticipated acquisition cost per unit of the HPFB-approved drug to the acquisition cost per unit of the FDA-approved drug. A SIP Sponsor could also compare the current retail cash price of the drugs. We seek comment on

these and other relevant measures that may be available to SIP Sponsors during proposal development.

We also seek comments on what mechanisms SIPs could use to ensure that there is a significant reduction in the cost of covered products to the American consumer and comments on what, if any, additional showing SIP Sponsors would need to make if the cost savings do not go directly to consumers. If the cost savings do not go directly to consumers directly because, for example, they accrue to a healthcare provider or payor, the SIP Proposal would need to show that there is a significant reduction in the cost of covered products to the American consumer.

We anticipate that some SIP Sponsors may seek to import drugs to be used by patients in State-run programs in which participants do not directly pay the cost of drugs. In such cases, a SIP Sponsor could submit information about whether cost-sharing expenses are reduced for the participants, or whether the program will result in cost savings that are passed on to consumers in other ways, such as increasing the number of people who can be covered by a State program, or increasing the availability of drugs covered by the program. We seek comment on this and on what other cost-related information SIP Sponsors could provide where drugs would be imported for use by patients in State-run programs.

The SIP Sponsor would be responsible for ensuring that the SIP and each entity that participates in the SIP complies with section 804, with other applicable sections of the FD&C Act, and with this and other applicable regulations for the entire length of the approval period. The SIP Sponsor should explain in detail how it will do so in the SIP Proposal.

2. Review and Authorization of Section 804 Importation Program Proposals

FDA will review and approve or deny SIP Proposals. We solicit comments on what the timeline for such review should be, and on what type and frequency of communication between

FDA and SIP Sponsors would be helpful and efficient. We also seek comment on whether SIP Proposals should be addressed on a first-come, first-served basis, or whether they should be prioritized. If they should be prioritized, we seek comment on what the basis for prioritization should be.

As noted previously, we recognize that at the time of submission, the SIP Sponsor may not know whether a drug meets the conditions in an FDA-approved NDA or ANDA. FDA will review, among other things, the information that the SIP Sponsor is able to provide about each of the drugs that the SIP Sponsor seeks to import to confirm that each is approved by both HPFB and FDA, that each FDA-approved drug is currently marketed in the United States, and that none of the drugs fall into any of the exclusions from the definition of eligible prescription drug. FDA will also review the proposal to ensure that the requirements of the FD&C Act and this rule are met, and specifically that the proposed supply chain, the proposed plan to relabel the eligible prescription drugs, and the proposed pharmacovigilance measures meet the requirements of the FD&C Act and this rule. FDA intends to call on other divisions of HHS, such as ASPE, to assist with the review and evaluation of the components of the proposal, and to refer questions to such divisions as appropriate, that relate to the price of the drugs to be imported and to the steps that will be taken to ensure that there is a significant reduction in the cost of drugs to consumers.

FDA and/or HHS may issue guidance on this topic as appropriate.

Where a SIP Proposal meets the requirements of section 804(b) through (h) of the FD&C Act and the requirements in the proposed rule, FDA may nonetheless decide, in its discretion, not to authorize the SIP Proposal. Among other reasons, FDA may decide not to authorize a SIP Proposal because of potential safety concerns with the SIP, because of the relative likelihood the SIP would not result in significant enough cost savings, or because FDA needs to limit the

number of authorized SIPs to effectively and efficiently run the program or in light of other resource demands.

3. The Section 804 Pre-Import Request

After FDA authorizes a SIP, the Foreign Seller can proceed to purchase one or more of the eligible prescription drugs included in the SIP Proposal directly from the manufacturer with the intent to sell them to the Importer. The Importer can then request that the manufacturer agree to conduct the testing set forth in section 804(d)(1)(J) and (L) of the FD&C Act. If the manufacturer declines to do so, the manufacturer must provide the information needed to conduct the testing, as required by section 804(e)(2) of the FD&C Act. The Importer can then submit a section 804 Pre-Import Request to the ESG or other transmission point identified by the Agency.

The Importer would need to submit a section 804 Pre-Import Request at least 30 days prior to the scheduled date of arrival of a shipment containing an eligible prescription drug(s) at the CBP port of entry authorized by FDA, or entry for consumption in ACE of one or more batches of an eligible prescription drug(s) covered by a SIP, whichever occurs first. FDA believes at least 30 days will be needed for FDA to sufficiently review the information provided. Under the proposed process, the Importer would not be permitted to ship an eligible prescription drug into the United States until a section 804 Pre-Import Request that includes that specific drug was granted by FDA.

Under the proposed rule (§ 251.5), a complete Pre-Import Request would include, at a minimum: identification of the Importer, including Importer name, business type (wholesale distributor or pharmacist), U.S. license number or numbers and State or States of license, business address, unique facility identifier if required to register with FDA as an establishment under section 510 of the FD&C Act or FDA establishment identification number if not required

to register as an establishment, and name of a contact person with their email and phone number; identification of the FDA-authorized SIP Proposal including the name of the SIP, the name or names of the SIP Sponsor and co-sponsors, if any, business address, and name of a contact person, with their email and phone number; identification of the Foreign Seller, including the name of the Foreign Seller, business address, unique facility identifier, any license numbers issued by Health Canada or a provincial pharmacy regulatory body, and the name of a contact person with their email and phone number; and identification and description of the eligible prescription drug or drugs covered by the Pre-Import Request including the following information: name of the HPFB-approved drug or drugs (established and/or trade), DIN, and complete product description including strength, description of dosage form, and route of administration; API information, including name of API, manufacturer of API and its unique facility identifier, and amount of API and unit measure in each eligible prescription drug; name (established and/or trade) of the FDA-approved counterpart drug or drugs and their NDA or ANDA number or numbers; manufacturer of the eligible prescription drug with the business address and unique facility identifier; copies of the invoice and any other documents related to the manufacturer's sale of the drugs to the Foreign Seller provided by the manufacturer to the Importer and copies of the same documents provided by the Foreign Seller to the Importer; quantity, listed separately by dosage form, strength, batch and lot or control number assigned by the manufacturer to each eligible prescription drug intended to be imported under this Pre-Import Request compared to the quantity of each batch and lot or control number originally received by the Foreign Seller from the manufacturer and the date of such receipt; expiration date of each HPFB-approved drug, listed by lot or control number; expiration date to be assigned to each eligible prescription drug when relabeled by the Importer with a complete description of how that

expiration date was calculated to comply with the FDA-approved drug's NDA or ANDA; NDC proposed for assignment by the Importer for each eligible prescription drug to be imported; and FDA product code for each eligible prescription drugs to be imported.

A Statutory Testing plan would also be part of the request, including: a description of how the samples will be selected from a shipment for the Statutory Testing; the name and location of the qualifying laboratory in the United States that will conduct the Statutory Testing; and if the importer will be conducting the Statutory Testing, or a description of the testing method(s) that will be used to conduct the Statutory Testing. If the manufacturer will be conducting the Statutory Testing, the description of the testing methods can be submitted by the manufacturer to FDA directly, as discussed later in this document. An attestation from the manufacturer, which is described in more detail later in this document, that, but for the fact that it bears the HPFB-approved labeling, the eligible prescription drug meets the conditions in the FDA-approved drug's NDA or ANDA, would also be included. If the manufacturer conducts the Statutory Testing, the manufacturer would need to provide the attestation to FDA. If the Importer conducts the Statutory Testing, the manufacturer would need to provide the attestation to the Importer.

Information related to the Importation would be provided, including the location of the eligible prescription drugs in Canada and anticipated date of shipment (date eligible prescription drug or drugs will leave their location in Canada); name, address, email, and telephone number of the foreign shipper; anticipated date of export from Canada and Canadian port of exportation; anticipated date of arrival at port(s) authorized by FDA to import eligible prescription drugs under section 804; the name, address, FDA establishment identification number, and telephone number of the warehouse, location within a specific FTZ, or other secure distribution facility

controlled by or under contract with the Importer where the eligible prescription drug(s) will be stored pending testing, relabeling, and FDA determination of admissibility; and information regarding the facility where the relabeling and any limited repackaging activities will occur for all eligible prescription drug(s) covered by this Pre-Import Request, including: (1) the facility's unique facility identifier; (2) the facility's name, address, and FDA establishment identification number; (3) the anticipated date the relabeling and any limited repackaging will be completed; and (4) information about where the relabeled drug will be stored pending distribution, including the FDA establishment identification number of the storage facility, if available.

FDA's grant of a section 804 Pre-Import Request does not constitute an admissibility determination by the Agency of any of the drugs covered by the Request. When a Pre-Import Request is granted by FDA, that Pre-import Request would cover subsequent shipments of the eligible prescription drug(s) identified in the Agency's grant of that Request provided that the rest of the information contained in the Pre-Import Request, with the exception of the anticipated dates of shipment and export, is the same. We seek comment on this approach.

When the Agency grants a section 804 Pre-Import Request, it will specify an FDA field laboratory to which the Importer would need to submit three sets of the samples that the Importer sends to the qualifying laboratory to enable FDA to conduct the Statutory Testing as FDA deems warranted.

4. Importation

When goods are imported into the United States, they must be *entered* at one of the CBP ports of entry (sea, land, rail, and air). The term *entry* generally refers to the information or documentation that an importer of record, or an authorized customs broker, must file with CBP

for importing merchandise into the United States. A SIP Importer will be, and must qualify as, the importer of record for eligible prescription drugs imported under section 804.

The proposed rule would require that an entry for consumption of an eligible prescription drug under an authorized SIP be filed electronically in ACE, or any other Electronic Data Interchange (EDI) system authorized by CBP. Currently, ACE is the sole EDI system authorized by CBP for electronic entry of FDA-regulated products. ACE serves as the “single window” through which an import filer submits the data elements required for an import entry, including data elements designated by a Partner Government Agency (PGA). As a PGA, FDA has designated a PGA Message Set in ACE for FDA-regulated products. This message set contains both required and optional data elements to assist us in our admissibility review of FDA-regulated articles. In the *Federal Register* of November 29, 2016 (81 FR 85854), FDA published a final rule, effective December 29, 2016, entitled “Submission of Food and Drug Administration Import Data in the Automated Commercial Environment,” which requires certain data elements that are material to our import admissibility review be submitted in ACE or any other EDI system authorized by CBP, at the time of entry. The rule was intended to facilitate automated “May Proceed” determinations by the Agency for low-risk FDA-regulated products which, in turn, allows the Agency to focus our limited resources on products that may be associated with a greater public health risk. The final rule is codified in subpart D, 21 CFR part 1.

All shipments containing eligible prescription drugs to be imported under an authorized SIP would need to arrive and be entered at the CBP port of entry that is authorized by FDA. When an entry for consumption containing an FDA-regulated product is processed by CBP, CBP relays the data in the PGA Message Set to FDA using an electronic interface with FDA’s import processing system, currently the Operational and Administrative System for Import Support

(OASIS). The import filer need only submit this entry information once in the ACE system, provided that the information submitted in ACE is accurate. ACE entries are electronically screened in OASIS against criteria developed by FDA. FDA's Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT) is a risk-based electronic screening tool for OASIS that performs this initial electronic screening to assist FDA entry reviewers by evaluating the potential risks associated with each article and identifying those articles that may present a higher public health risk for further examination by FDA.

As discussed, the drugs covered by a SIP can be imported using two proposed pathways: admission to an FTZ with later entry for consumption and filing in ACE when compliant, or filing an entry for consumption in ACE with a request to bring the eligible prescription drugs into compliance with the FD&C Act under section 801(b) of the FD&C Act and § 1.95. The plan submitted under §§ 1.95 and 1.96 for the drugs would need to include the testing and relabeling required under this proposed rule.

FDA proposes that the testing and relabeling of a shipment, as described in the Section 804 Pre-Import Request, take place after the shipment has arrived in the United States, but before it can be distributed in the United States. This will enable the Importer to inspect the Canadian labeling and packaging as part of its screening obligations. It will also place the responsibility on the Importer to ensure that the samples submitted for testing are representative of the actual shipment. The Importer will also be responsible for ensuring that the relabeling and the product identifier are compliant with U.S. laws and regulations after FDA has determined that the testing results are acceptable and before an eligible prescription drug is sold in the United States. Placing these responsibilities on Importers will aid FDA in its efforts to monitor compliance with and enforce the requirements of the FD&C Act and this proposed rule when it is finalized.

As discussed earlier, under the proposed rule, an Importer could admit an eligible prescription drug to an FTZ in the United States for the purpose of completing the required testing and relabeling. An FTZ is a secure area under the supervision of CBP. FTZs were established in the United States under the Foreign Trade Zones Act of 1934 (19 U.S.C. 81a-81u) for importers to hold or otherwise manipulate goods without being subject to certain CBP requirements including customs entry (articles are “admitted” to an FTZ and not entered), payment of duty, tax, or bond. Since these FTZ Act exclusions only affect the application of certain CBP laws, FDA-regulated articles that are brought into an FTZ remain subject to other U.S. laws and regulations affecting imported goods. Therefore, placement of eligible prescription drugs in an FTZ does not affect FDA’s jurisdiction and inspectional authority over them. Samples of the eligible prescription drug or drugs can be removed from the FTZ for the purpose of the required testing by a qualifying laboratory and for providing samples to FDA as proposed in this rule.³

If the Importer pursues the second pathway, filing an entry for consumption in ACE and requesting to bring the drugs into compliance, under section 801(b) of the FD&C Act, the Importer would submit Form FDA 766, to the relevant FDA Imports Division Director. After review, the Director would notify the Importer of FDA’s approval or disapproval of the plan to bring the drugs into compliance. If approved, the FDA notice of approval will specify the conditions to be fulfilled and the time limit for fulfilling them (see § 1.96). Under the proposed rule, the Importer would need to keep the product at a designated secured warehouse, and under appropriate environmental conditions to maintain the integrity of the products, until FDA issues an admissibility decision. The secured warehouse would need to be within 30 miles of the

³ Any such samples removed from the FTZ for testing in the customs territory of the United States will have to be entered using normal Customs procedures.

authorized Port of Entry to facilitate FDA oversight, including the collection and examination of samples.

After the authorized plan has been completed, the Importer will complete the section entitled “Importer’s Certificate” on Form FDA 766 and provide that certification to the relevant FDA Imports Division Director. At this point, FDA may choose to conduct a followup inspection and/or sampling to determine compliance with the terms of the authorized plan. If FDA determines that the conditions of the authorized plan have been fulfilled, the Agency will notify the Importer through a Notice of Release indicating that the admissible portion of the shipment is no longer subject to detention or refusal of admission. This Notice is usually identified as “Originally Detained and Now Released.” A copy of the Notice is sent to the owner or consignee; CBP would then be notified electronically of FDA’s “May Proceed” determination. If there is a non-admissible portion of the shipment, that portion can be destroyed, or re-exported by the Importer under FDA or CBP supervision (21 U.S.C. 381(a)). A Notice of Refusal of Admission will be issued to the Importer for the rejected portion.

Under the proposed rule, FDA would intend to refuse admission into the United States under section 801(a)(3) of the FD&C Act if: (1) 6 months have passed since the entry date of the shipment; (2) the conditions of the SIP or the section 804 Pre-Import Request are not met; or (3) the drug otherwise appears to be adulterated, misbranded or unapproved in violation of section 505 of the FD&C Act. If FDA refuses admission into the United States under section 801(a)(3) of the FD&C Act, the drug should be exported or destroyed by the Importer within 90 days of the refusal.

The proposed rule would require that an entry for consumption be made electronically in ACE for any shipment containing an eligible prescription drug. The port of arrival and port of

entry would be limited to a CBP port that is authorized by FDA, so that FDA can ensure that it has adequate resources at the port to process the arrival and entry of shipments that contain an eligible prescription drug and to perform sampling of any such shipment, if necessary. The following data elements would be required to be submitted in ACE at the time of entry:

- a. The unique facility identifier of the Foreign Seller;
- b. The Importer's NDC for each eligible prescription drug;
- c. The NDA or ANDA number of each eligible prescription drug's FDA-approved counterpart;
- d. The lot or control number assigned by the manufacturer for each eligible prescription drug;
- e. The FDA Quantity, which is the quantity of the eligible prescription drug or drugs in an import line delineated by packaging level, including the type of package from the largest packaging unit to the smallest packaging unit; the quantity of each packaging unit; and the volume and/or weight of each of the smallest of the packaging units; and
- f. The Pre-Import Request number

FDA would require submission of these data elements in ACE at the time of entry to facilitate the importation of eligible prescription drugs as part of a SIP. The proposed rule would clarify that for eligible prescription drugs the unique facility identifier of the registered Foreign Seller and the NDC proposed for assignment by the Importer be submitted in ACE at the time of entry. The application number of the NDA or ANDA for the FDA-approved drug that is the counterpart of the eligible prescription drug would also be submitted in ACE. This information will help FDA to verify that an entry for consumption contains eligible prescription drugs. The lot or control number of each eligible prescription drug would be required to be submitted by the

Importer to FDA under this proposed rule, in accordance with section 804(d)(1)(H) of the FD&C Act.

In accordance with section 804(d)(1)(D) of the FD&C Act, we propose to require the Importer submit information on the quantity of the eligible prescription drug that is shipped in ACE at the time of entry. FDA is proposing to require that quantity include the quantity of each layer/level of packaging of the eligible prescription drug(s); the unit of measure, which is the description of each type of package; and the volume and/or weight of each of the smallest of the packaging units. The quantity would be required to be submitted in decreasing size of packing unit (starting with the outermost/largest package and ending with the innermost/smallest package).

Information on the quantity of each layer or level of packaging will help the Agency identify an article being imported or offered for import as an eligible prescription drug. Although CBP and FDA utilize Harmonized Tariff Schedule codes to generally identify which imports are subject to an FDA admissibility review, these codes are often not sufficient to specifically identify a product for FDA decision making. There may be instances in which a drug's packaging does not meet the conditions of the approved NDA or ANDA. Packaging can affect the safety of an FDA-regulated product, for example, where an article is represented as "sterile." Submission of the quantity, including of each layer or level of packaging, in ACE at the time of entry would assist the Agency should it need to perform field examinations, label examinations, sample collections, detentions, or refusals.

Finally, the Pre-Import Request number, which FDA would provide to the Importer when we grant the Pre-Import Request, would allow FDA's review staff to verify that a Pre-import Request covering the eligible prescription drugs in the shipment has been approved by FDA.

5. Submission and Review of Testing Results

Once the testing described in section 804(d)(1)(J) and (L) of the FD&C Act is complete, the results would be submitted to FDA, along with a Certificate of Analysis (COA), selection method for the samples, the testing methods used, laboratory records required by the proposed rule in accordance with section 804(d)(1)(L), and any other documentation demonstrating that the testing was conducted at a qualifying laboratory and otherwise meets the requirements in section 804(e)(1) of the FD&C Act. If the Importer performs the Statutory Testing after the shipment has been admitted to an FTZ but before filing entry for consumption, the Importer would be required to submit the required testing results and records to FDA in electronic form to the ESG or to an alternative transmission point identified by FDA, prior to relabeling the drugs. If the Importer performs the testing at a qualifying laboratory as part of an FDA-approved plan under §§ 1.95 and 1.96, the Importer would be required to submit the required testing results and records as part of the Importer's plan prior to relabeling of the drugs. If a manufacturer performs the Statutory Testing, the manufacturer would submit the test results and records to FDA directly in electronic form to the ESG or to an alternative transmission point identified by FDA. FDA would review the test results and records and notify the Importer whether the test results are acceptable to the Agency and then the Importer would cause the drugs to be relabeled in accordance with the proposed rule. Under the proposed rule, if the data and information that the manufacturer or Importer submits do not establish that the drug the SIP Sponsor seeks to import is authentic, not degraded, and meets the conditions of an FDA-approved NDA or ANDA, the drug cannot be relabeled, and FDA would refuse admission of the drug. FDA proposes to require that the relabeling only take place after the Agency has accepted the test results to avoid potential diversion that could occur if eligible prescription drugs are relabeled for the U.S.

market and then fail the testing requirements, which could happen before or after export of the refused drugs to Canada.

6. Period of Authorization of Section 804 Importation Programs

Under the proposed rule, SIPs would initially be authorized for a 2-year period, with the possibility of extensions for additional 2-year periods. Each 2-year period would begin when the Importer files an electronic import entry for consumption for its first shipment of drugs. If the Importer does not file an electronic import entry for consumption for a shipment of eligible prescription drugs within 1 year of the date the SIP is authorized by FDA, the SIP Sponsor would have to submit, and FDA would have to authorize, a new SIP Proposal before it could begin the importation process.

We believe that SIPs should be given a 2-year period before re-authorization is required to continue in the program because we believe that this will provide sufficient time for SIP Sponsors to demonstrate that they can in fact import drugs from Canada with no additional risk to the public's health and safety and that such importation in fact results in a significant reduction in the cost of covered products to the American consumer. We believe that SIPs should terminate after 2 years unless re-authorized because importation under section 804 is novel. After 2 years, we will have the data necessary to evaluate a SIP's success. We will be able to determine if the safeguards in section 804 of the FD&C Act and in this rule, should it be finalized, are working and, if they are, if there are requirements that could be amended or streamlined. We will be able to compare and contrast the approaches taken by different SIP Sponsors. FDA will also take the opportunity to assess any changes in the marketplace that result from section 804 importation. For example, we will be able to determine whether section 804 importation resulted in changes in the price or supply of drugs in Canada or the United

States, whether there are newly erected or existing barriers to section 804 importation, and whether and how bad actors respond to section 804 importation. FDA seeks comment on this approach, including whether 2 years is the appropriate initial period of time for a SIP, whether 2-year re-authorization periods are appropriate, and whether there should be a limit on the number of re-authorization periods.

7. Modification or Extension of Section 804 Importation Programs

Under the proposed rule, if a SIP Sponsor wishes to make a change to an authorized SIP (for example, to amend the list of eligible drugs it seeks to import or to work with a different Foreign Seller, Importer, or qualifying laboratory), the SIP Sponsor would be required to submit a supplemental proposal for FDA's consideration. As noted earlier, if a SIP Sponsor wishes to work with more than one Foreign Seller or Importer, it must first demonstrate that it has consistently imported eligible prescription drug(s) in accordance with section 804 and this rule. We generally expect that a SIP Sponsor would have submitted its first quarterly report to FDA before it submits a supplement to the SIP Proposal seeking to add an additional Foreign Seller or Importer.

If FDA authorizes the supplemental proposal, a new Pre-Import Request would be required for the next shipment. Under the proposed rule, a SIP Sponsor would not be permitted to make any changes or permit any changes to be made to the SIP without first securing FDA's authorization.

Under the proposed rule, an authorized SIP Sponsor would be able to submit a proposal asking for authorization to extend the SIP for additional 2-year-long periods beyond the initial 2-year long implementation period. To be eligible for extension, a SIP would need to be up to date on all the information and records-related requirements of section 804 and this rule. A request

for authorization to extend a SIP should be submitted at least 3 months before the SIP's 2-year-long authorization period expires.

8. Denial, Suspension, or Revocation of Authorization of Section 804 Importation Programs

If at any point in the course of its review of a SIP Proposal, FDA finds minor, correctable deficiencies, the Agency intends to make a reasonable effort to promptly communicate them to the SIP Sponsor so that they can be corrected in a timely way. However, FDA may deny a request for authorization, modification, or extension of a SIP in its discretion, as described elsewhere in this proposed rule, including if a proposed SIP does not meet the standard for authorizing a SIP under this proposed rule.

Under the proposed rule, FDA can revoke the authorization of a SIP in whole or in part, including with respect to one or more drugs in the SIP, at any time for any reason in FDA's discretion, including if, for example: (1) FDA finds that the SIP Proposal contained an untrue statement of material fact or omitted material information required by this part; (2) the SIP no longer meets the requirements of section 804 of the FD&C Act or the standard for authorizing a program under this proposed rule; (3) continued implementation of the SIP will pose additional risk to the public's health and safety; (4) continued implementation of the SIP will not result in a significant reduction in the cost of covered products to the American consumer; or (5) continued monitoring of the SIP imposes too much of a drain on Agency resources or is inconsistent with the Agency's prioritization of resources.

Under the proposed rule, if at any point a SIP Sponsor has reason to suspect that a drug, manufacturer, Foreign Seller, Importer, qualifying laboratory, or other participant in or element of the supply chain that FDA initially authorized does not in fact meet the requirements of section 804 or any other applicable requirements of the FD&C Act, or of any applicable

regulation, including this rule, the SIP Sponsor would be required to stop importation immediately, notify FDA, and demonstrate to FDA that importation has in fact been stopped pending an investigation. In addition, FDA may also suspend a SIP under such circumstances, or under other circumstances in FDA's discretion, which would prevent further importation of drugs under it. Under certain circumstances set forth in section 804(g) of the FD&C Act, FDA is required to suspend importation. Section 804(g) provides that the Secretary shall require that importations of a specific prescription drug or importations by a specific importer under subsection (b) be immediately suspended on discovery of a pattern of importation of that specific prescription drug or by that specific importer of drugs that are counterfeit or in violation of any requirement under this section, until an investigation is completed and the Secretary determines that the public is adequately protected from counterfeit and violative prescription drugs being imported under subsection (b).

In addition, under the proposed rule, where a SIP Sponsor fails to timely extend its authorized SIP, the SIP would be considered expired. The sponsor of an expired SIP would need to submit a new SIP Proposal because FDA may be unable to confirm that the SIP Sponsor continues to meet all the necessary requirements. FDA is also proposing to terminate a SIP upon request from the SIP Sponsor when the request includes a notice of the SIP Sponsor's intent to discontinue its activities. The sponsor of an expired SIP would be required to submit a new SIP Proposal should it decide to resume section 804 importation activities.

9. Monitoring and Compliance

SIP Sponsors will be responsible for ensuring that all the participants in a SIP comply with the requirements of section 804 of the FD&C Act and this rule. As noted earlier, a SIP Sponsor would need to develop a compliance plan and describe it in detail in their SIP Proposal

for FDA’s review and authorization. We ask for comment on what elements should be included in a SIP’s compliance plan. Among other things, such a plan could require: (1) a description of the division of responsibilities between co-sponsors, if any, (2) the creation of written compliance policies, procedures, and protocols; (3) the provision of education and training to ensure that Foreign Sellers, Importers, qualifying laboratories, and their employees understand their compliance-related obligations; (4) the creation and maintenance of effective lines of communication, including a process to protect the anonymity of complainants and to protect whistleblowers; and/or (5) the adoption of processes and procedures for uncovering and addressing noncompliance or misconduct. We seek comment on what alternate or additional requirements might be appropriate if a SIP is co-sponsored.

FDA’s usual compliance and enforcement tools apply to SIP participants. We will retain our usual rights to conduct pre-authorization, surveillance, and risk-based inspections under section 704 of the FD&C Act. In addition, the proposed rule would require that SIP Sponsors and other SIP participants agree to submit to audits of their books and records and inspections of their facilities as a condition of participation in a SIP. If a SIP Sponsor, manufacturer, Foreign Seller, Importer, qualifying laboratory, or other participant in or element of the supply chain delays, denies, or limits an inspection, or refuses to permit entry or inspection of their facility or their records, any drug that they have held would be deemed to be adulterated (FDA, 2014. “Guidance for Industry: Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection.” (Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/circumstances-constitute-delaying-denying-limiting-or-refusing-drug-inspection>). FDA could also suspend the SIP, in whole or in part, immediately in that circumstance.

FDA can take action through, e.g., warning letters, seizure, and detention, to address failure to abide by applicable requirements, including requirements in this rule, when finalized, and requirements concerning product quality. FDA would also retain the authority under section 801 of the FD&C Act to refuse admission to a drug that does not comply with the FD&C Act or the rule, including, under section 801(a)(3) of the FD&C Act, the authority to refuse entries of drugs that appear to be adulterated, misbranded, including if it does not comply with the product identifier requirement of section 582 of the FD&C Act, or in violation of section 505 of the FD&C Act.

D. Requirements for Foreign Sellers

A “Foreign Seller” under section 804 and this proposed rule is an establishment within Canada engaged in the distribution of an eligible prescription drug that is imported into the United States. Under the proposed rule, the Foreign Seller would buy eligible prescription drugs directly from the manufacturers and then sell them directly to the Importer. The Foreign Seller would also be responsible for relabeling the drug product solely to affix or imprint the SSI on each package and homogenous case of the eligible prescription drug(s).

The SIP Sponsor would be required to ensure that the Foreign Seller meets all the licensing and registration requirements set forth in the statute and this proposed rule. We propose to require that Foreign Sellers have an active drug establishment license as a wholesaler from Health Canada. We also propose to require that they be registered with provincial pharmacy regulatory authority to distribute HPFB-approved drugs. In addition, we propose that a Foreign Seller could not be licensed to distribute drugs that are approved by countries other than Canada and that are not HPFB-approved for distribution in Canada. We believe that this is an important safeguard that will help ensure that only HPFB-approved drugs are imported to the

United States under SIPs. We seek comment on what additional standards should be imposed or qualifications required of Foreign Sellers.

The proposed rule would also require Foreign Sellers to register with FDA. Section 804(f) of the FD&C Act requires that any establishment within Canada engaged in the distribution of a prescription drug that is imported or offered for importation into the United States shall register with the Secretary the name and place of business of the establishment and the name of the U.S. agent for the establishment. This proposed rule implements that provision and largely tracks the registration requirements for foreign establishments set forth in 21 CFR 207.21, 207.25, and 207.29.

Facilities that register with FDA as Foreign Sellers should do so using the existing structured product labeling (SPL) format used by establishments required to register under section 510 of the FD&C Act. FDA intends to create a new business operation code for Foreign Sellers, “Section 804 Foreign Seller.” After the initial registration, a facility registered with FDA as a Foreign Seller would also be required to register annually for each year thereafter in which it wishes to remain a Foreign Seller, during the registration period between October 1 and December 31. We propose to require in this rule that a Foreign Seller’s registration include its name, place of business, unique facility identifier, Health Canada Drug Establishment License number, point of contact email address and telephone number, the name of its U.S. agent, the name of each SIP with which it works, and any other information that FDA may decide is necessary.

U.S. agents of Foreign Sellers would be subject to the same requirements as agents of foreign registrants are under 21 CFR 207.69(b). Their responsibilities would include responding to communications and questions from FDA and helping FDA to schedule inspections. Under

the proposed rule, in certain circumstances, FDA may provide information and/or documents to the U.S. agent, which would be considered equivalent to providing the same information and/or documents to the Foreign Seller.

We note that as an entity that holds drugs, the Foreign Seller would be subject to FDA inspection under section 704 of the FD&C Act.

E. Requirements for Importers

Under section 804, an Importer is defined as a pharmacist or a wholesaler. Under the proposed rule, if finalized, to be part of a SIP, an Importer would need to be duly licensed as a pharmacist by the State in which the Importer is located and in which it does business, or duly licensed as a wholesaler. In addition, the Importer's pharmacist or wholesaler licenses would need to be in effect (i.e., not expired), and the Importer must be in good standing with the licensor. Furthermore, the Importer would need to be the U.S. owner of an eligible prescription drug at the time of entry or arrival of the drug into the United States.

We note that the Importer has a number of responsibilities under section 804 and this rule, including screening eligible prescription drugs for evidence regarding whether or not they are adulterated, counterfeit, damaged, tampered with, or expired; arranging for each shipment of eligible prescription drugs to be tested by a qualifying laboratory; and arranging for them to be relabeled with the FDA-approved labeling, including the carton and container labels, prescribing information, and any patient labeling, such as medication guides, instruction for use documents, and patient package inserts. The Importer is also responsible for facilitating the affixation or imprinting of a product identifier at the same time that the eligible prescription drugs are relabeled with the FDA-approved labeling.

We propose that the screening conducted by the Importer would include examination of the Canadian labeling of a sample of each shipment of section 804 drugs to verify that the labeling is consistent with that of an HPFB-approved drug and that the drugs have been serialized as prescribed in the proposed rule, when finalized. The screening could also include a visual comparison of a sample of the section 804 drug to a sample of the HPFB-approved drug. We seek comment on the feasibility and sufficiency of this screening, as well as on what additional or alternative screenings that the Importer could do to ensure that imported eligible prescription drugs are not adulterated, counterfeit, damaged, tampered with, or expired.

If an Importer will be relabeling the drug itself, the Importer must also be registered with FDA under section 510(b) of the FD&C Act and obtain a labeler code from FDA under § 207.33(c) (21 CFR 207.33(c)). If the Importer chooses to contract with a separate entity (e.g., a repackager or relabeler) to relabel the drug on its behalf, the Importer will be a private label distributor, as that term is defined in § 207.1 (21 CFR 207.1), because it will be commercially distributing under its own label drugs that it did not itself manufacture, repackage, or relabel. As noted elsewhere in this proposed rule, a repackager or relabeler acting on an Importer's behalf would only repackage to the extent it is required to label the drug. As a private label distributor, the Importer will not be required to register with FDA, but it must obtain its own labeler code from FDA, under § 207.33(c). Under the proposed rule, the NDCs for the section 804 drugs that are relabeled by an entity other than the Importer would nonetheless incorporate the Importer's labeler code. Among other requirements, before an eligible prescription drug can be released into interstate commerce it will need a new NDC and will need to be listed. We note that a drug imported under section 804 of the FD&C Act will have a different NDC than its FDA-approved counterpart. Under the requirements proposed in this rule, if the Importer is also a repackager or

relabeler, it will be the Importer's responsibility to propose an NDC for assignment for each eligible prescription drug under § 207.33. Under these circumstances, the Importer will also be responsible for listing each eligible prescription drug under § 207.53 (21 CFR 207.53). If the Importer is a private label distributor, it would be the Importer's responsibility to ensure that the entity relabeling an eligible prescription drug on its behalf proposes an NDC under § 207.33 and lists each eligible prescription drug under § 207.53.

The Importer, or authorized customs broker, would also be responsible for filing an entry for consumption in ACE for the drugs to be imported through a CBP port of entry designated in a SIP Proposal authorized by FDA. In addition, Importers would be required to collect and submit to FDA the information and documentation about the imported drug that is set forth in section 804(d) of the FD&C Act as discussed later. Importers also would have responsibilities related to adverse event, medication error, field alert reports, and other reports, and related to drug recalls.

We seek comment on whether there are qualifications Importers should be required to have, beyond being licensed as a pharmacist or wholesaler, given their responsibilities.

F. Supply Chain Requirements

When Congress enacted section 804 of the FD&C Act in 2003, FDA's authority with respect to drug supply chain security was more limited than it is today. In 2013, Congress enacted the DSCSA, which strengthened FDA's authority to protect the security and integrity of the drug supply chain. Specifically, section 582 of the FD&C Act, as added by the DSCSA, establishes the product identification, verification, and tracing requirements that manufacturers, wholesale distributors, pharmacists, and other trading partners must adhere to for covered transactions involving certain prescription drugs. Because the DSCSA did not include an exemption for drugs imported under section 804 of the FD&C Act, such drugs are subject to the

requirements in section 582 of the FD&C Act. We recognize, however, that certain requirements in section 582 may be difficult or impossible for such drugs to meet. Accordingly, under the authority provided by section 582(a)(3)(A)(iii) of the FD&C Act, FDA proposes to exempt from section 582 certain transactions for drugs imported under section 804 of the FD&C Act.

Under section 804(c)(3), this proposed rule may contain “any additional provisions determined by the Secretary to be appropriate as a safeguard to protect the public health or as a means to facilitate the importation of prescription drugs.” To ensure the proposed exemptions from section 582 of the FD&C Act do not compromise the security of the supply chain for drugs imported under section 804 of the FD&C Act, this rule also proposes additional provisions to safeguard the public health. These additional safeguards are necessary for the Secretary to certify that implementation of section 804 of the FD&C Act would pose no additional risk to the public’s health and safety.

First, if an eligible prescription drug is manufactured outside of Canada, it would need to be exported commercially into Canada by the manufacturer and labeled for the Canadian market. It could not be transshipped through Canada for sale in another country because this could create opportunities for counterfeiting or other forms of fraud.

Second, an eligible prescription drug would need to be sold by the manufacturer directly to a Foreign Seller in Canada. FDA has determined that this requirement is critical because FDA would generally not possess information needed to trace drug products labeled for the Canadian market back to the original manufacturer. As discussed further in the “Supply Chain Security Requirements” section below, for products and transactions that are subject to the DSCSA, supply chain protections are in place to allow for tracing products up to the manufacturer at the package and homogenous case level.

Under FDA's general proposed approach, a Foreign Seller would then ship the drug directly to the Importer in the United States. We considered whether to propose allowing more than one Foreign Seller in the Canadian supply chain but decided against this approach because we do not believe it would be possible for a SIP Sponsor to demonstrate that the same level of safety would be assured. For a SIP to pose no additional risk, it would have to match the protections of the DSCSA through other means. The short supply chain, coupled with this proposed rule's other provisions like serialization and testing, would permit control over and transparency into the supply chain to help ensure comparable safety. Therefore, we propose to require that each Foreign Seller buy the drug directly from the manufacturer and then sell it directly to the Importer in the United States because this would minimize supply chain security risks, including the risks posed by increased opportunities for counterfeiting and other forms of fraud that obscure the origin of drugs imported under section 804 of the FD&C Act. As the number of entities outside the United States that handle the drugs increases, the supply chain becomes progressively less transparent and more vulnerable to risk. The proposed short supply chains would also allow FDA and States to supervise the supply chain participants more closely. This rule proposes additional safeguards on tracing products through the pre-U.S. supply chain, which we believe will result in a level of supply chain security that poses no additional risk to the public's health and safety, but these proposed provisions are premised on the presence of just one Foreign Seller per supply chain. Allowing for additional Foreign Sellers in a supply chain would undermine our ability to ensure that our proposed approach poses no additional risk.

Although we cannot foresee at this time how a longer supply chain would not pose additional risk to the public's health and safety, we seek comment on whether there actually are safeguards that could be put in place that would enable FDA to authorize a SIP with multiple

Foreign Sellers in a single supply chain in Canada. Such comments should provide specific details regarding the additional safeguards and how they would provide the same level of protection to the supply chain. If, in response to comments, we determine that FDA could authorize a SIP with more than one Foreign Seller in a single supply chain because we are able to adopt additional safeguards such that the SIP would pose no additional risk to the public's health and safety, we would consider having the final rule account for this possibility. For example, we could revise §§ 251.3, 251.14(a)(4), 251.19(c), and 251.19(d)(2), as follows.

- Section 251.3 could be revised to state that, in its initial proposal, a SIP Sponsor must only designate one Foreign Seller and one Importer that may engage in the distribution of any drug specified in the proposal, unless the SIP Sponsor demonstrates that the SIP will meet additional safeguards, which would be detailed in the final rule, necessary to ensure that the inclusion of subsequent specified Foreign Sellers would pose no additional risk to the public's health and safety.
- Section 251.14(a)(4) could be revised to state: "For each drug imported under the SIP, the drug is only shipped by the entities that are specified in the SIP."
- Section 251.19(c) could be revised to state: "The Importer must also confirm that the eligible prescription drug was bought directly from the manufacturer by a Foreign Seller, and that all subsequent sales of that eligible prescription drug, up to and including the sale to the Importer, were made only among Foreign Sellers described in the SIP."
- Section 251.19(d)(2) could be revised to state: "documentation demonstrating that the eligible prescription drug was only handled by the manufacturer and Foreign Seller(s) described in the SIP before the Importer received the drug;"

In addition, among other potential revisions that may be necessary, if the final rule were to permit longer supply chains, we would include in the final rule those additional safeguards--submitted in comments justifying an allowance for multiple Foreign Sellers in a single supply chain--that would be applicable to most, and perhaps all, proposals that include multiple Foreign Sellers. We note that other requirements would apply as well that would need to be specified in the final rule, including the testing requirements described in section 804(d)(1)(J)(ii).

Under the proposed rule, following the shipment into the United States, the Importer would be responsible for: (1) sending FDA information about the drug, including information it receives from the Foreign Seller and the test results from the qualifying laboratory and also for (2) ensuring that the drug is relabeled with the required U.S. labeling and DSCSA product identifier. The Importer would then sell the product to either another entity in the United States (if it is a wholesaler) or dispense the product itself to patients (if it is a pharmacist).

We acknowledge that there are certain assurances regarding authenticity and quality when a manufacturer manufactures drugs intended for sale in the United States. We seek comment on the approach in this proposed rule and whether it contains sufficient safeguards to ensure that the proposed importation poses no additional risk to health or safety.

1. Foreign Seller's Supply Chain Security Obligations

Once the Foreign Seller receives product from a foreign manufacturer, which would be entirely intended and labeled for sale in the Canadian market, the Foreign Seller would need to separate the portion of product it intends to sell to the Importer in the United States under section 804, and maintain that portion in a separate area in its facility from the portion intended for the Canadian market. We anticipate that the volume of drug included in the portion intended for the U.S. market will be agreed upon between the Foreign Seller and the Importer to whom it will sell

the drug, and that such volume will be identified in a contract agreement and in records that the Importer is obligated to send to FDA under section 804(d) of the FD&C Act.

Under the proposed rule, for the portion of drug that will be transacted between the Foreign Seller and the Importer under section 804, the Foreign Seller would need to assign an SSI to each package and homogenous case of drug in that portion. The rule proposes that “package” means the smallest individual salable unit of product for distribution that is intended by the Foreign Seller for sale to the Importer located in the United States, and that “individual saleable unit” means the smallest container of product sold by the Foreign Seller to the Importer. The rule proposes that an “SSI” consists of a unique alphanumeric serial number of up to 20 characters. Using a stamp or adhesive sticker, the Foreign Seller would be required to place the SSI on each package and homogenous case, but would not otherwise repackage or relabel the drug. If the product already contained a manufacturer-affixed DSCSA-compliant product identifier at the time the Foreign Seller receives it, the Foreign Seller would not be required to assign an SSI to the product before further engaging in a transaction with the Importer.

Under the proposed rule, the Foreign Seller would need to maintain records identifying its process for serializing and affixing the SSI onto each package and homogenous case, including an explanation of the controls in place to ensure the stamp or adhesive sticker is properly affixed. The Foreign Seller would also be required to adhere to all applicable good manufacturing practice requirements in accordance with section 501(a)(2)(B) of the FD&C Act and part 211. The SSI would need to occupy blank space on the package and homogenous case, and not obscure any other labeling information, including the manufacturer-labeled Canadian DIN that was on the package and homogenous case at the time the Foreign Seller received the product from the manufacturer. Therefore, a drug without a DIN would not be an eligible

prescription drug that could be imported into the United States. Finally, the Foreign Seller would need to maintain records associating the SSI with the DIN and all the records it received from the manufacturer upon receipt of the original shipment intended for the Canadian market.

The rule also proposes that various verification requirements on a Foreign Seller, that correspond, where applicable, with those provisions pertaining to a “manufacturer” under the DSCSA in section 582(b)(4)(A) through (C) of the FD&C Act. Specifically, the Foreign Seller would need to verify that a drug was not a suspect or illegitimate foreign product and would need to send information to the Importer about the purchase of the drug. “Suspect foreign product” and “illegitimate foreign product” are proposed in the rule as defined terms relating to the product that the foreign seller purchases from the manufacturer and align with the definitions of “suspect product” and “illegitimate product” in DSCSA. In addition, the Foreign Seller would need to be able to respond to requests for verification from FDA or others within 24 hours or in other such reasonable time as determined by FDA based on the circumstances of the request. We seek comment on the scope of the foreign seller’s proposed verification responsibilities, and the extent to which Foreign Sellers currently or in the future may have systems or processes in place to meet such requirements.

Under the proposed rule, the Foreign Seller would not be engaged in repackaging, only relabeling, and it would be receiving a product from the original manufacturer that is not DSCSA-compliant, since that product would have been intended and labeled entirely for the Canadian market. To address potential risks, this rule proposes to impose several requirements on Foreign Sellers. For example, as noted above, the Foreign Seller would need to be registered with FDA under section 804 of the FD&C Act. Additionally, the rule proposes that, prior to or at the time of each transaction with the Importer in which the Foreign Seller transfers ownership

of the product to the Importer, the Foreign Seller would need to provide the Importer with a statement and information that is comparable with transaction information and transaction statement as defined in section 581(26) and (27) of the FD&C Act, respectively. Specifically, the Foreign Seller would be required to provide to the Importer:

- The proprietary or established name of the product;
- Strength and dosage form of the product;
- The container size;
- The number of containers;
- The lot number of the product;
- The date of the transaction;
- The date of the shipment, if more than 24 hours after the date of the transaction;
- The business name and address of the person associated with the Foreign Seller from whom ownership is being transferred;
- The business name and address of the person associated with the Importer to whom ownership is being transferred;
- The SSI for each package and homogenous case of product; and
- The Canadian DIN for each product transferred.

These requirements would be in addition to the statutory requirement under section 804(d)(1)(G) of the FD&C Act that the Importer obtain from the Foreign Seller, and submit to FDA, documentation specifying the original source of the prescription drug (i.e., identifying the original foreign manufacturer) and the quantity of each lot of the drug the Foreign Seller originally received from the manufacturer. The rule also proposes that the Foreign Seller would be required to send information to FDA and other officials as appropriate and upon request. For

example, upon a request by FDA, or other appropriate Federal or State official, in the event of a recall or for purpose of investigating a suspect product or an illegitimate product, the Foreign Seller would need to promptly provide the official with the information about the transaction with the Importer. This is comparable to the requirement for repackagers under section 582(e)(1)(C) of the FD&C Act; other DSCSA trading partners currently have similar obligations.

The required activities of the Foreign Seller proposed in this rule, as described above, presume a single Foreign Seller between the manufacturer and Importer in a particular supply chain. However, as noted above, if in response to comments, we determine that additional safeguards exist such that a SIP with a subsequent Foreign Seller or Foreign Sellers in a supply chain could be proposed to ensure that the longer supply chain would not pose additional risk to the public's health and safety, we would consider having the final rule account for this possibility. Our analysis of comments received will include a consideration of how the requirements described above on the single Foreign Seller (e.g., to place an SSI on products, send transaction information to the Importer, verify products, and maintain records) would be applied to subsequent Foreign Sellers in a supply chain.

In sum, we have determined that a Foreign Seller would need to be capable not only of registering with FDA per section 804(f) of the FD&C Act and sharing relevant information and records with the Importer per section 804(d)(1)(G) of the FD&C Act, but also of preserving supply chain security and sending package-level information about the product they are selling to the Importer in a format that enables interoperability. This is consistent with section 804(c) of the FD&C Act, which permits the Secretary to include any additional requirements determined to be appropriate as a safeguard to protect the public health. Without these requirements, the

Secretary would not be able to make the certification required under 804(l) that importation poses “no additional risk to the public’s health and safety.”

2. Importer’s Supply Chain Security Obligations

Under the proposed rule, when the Foreign Seller sends a shipment of the product to the Importer, the product would need to include the Foreign Seller-affixed SSI, and, as noted earlier, contain the original Canadian labeling that the manufacturer had applied to the drug. The Importer would be responsible for relabeling the product with the required U.S. labeling.

If the Importer intends to place the product into further transactions in commerce, that relabeling would also need to include placing or affixing a product identifier that is associated with the SSI that the Foreign Seller assigned to the product prior to sending it to the Importer. Therefore, as part of the relabeling, this rule proposes that the Importer is responsible for affixing or placing a product identifier, as that term is defined in section 581(14) of the FD&C Act, on each package and homogenous case of product that it receives from the Foreign Seller. If, however, the Importer intends to directly administer the product to patients, as may be the case if the Importer intends to dispense the drug as a pharmacist, a product identifier would not be required to be affixed or imprinted on each package and homogenous case of the eligible prescription drug.

To avoid unnecessary steps in the supply chain, the product identifier would need to be affixed or imprinted at the same time at which the drug is being relabeled with the required U.S. labeling. As proposed, the Importer may relabel the product itself, or may choose to contract with a separate entity to relabel on its behalf. In either case, the entity that relabels the product must be registered with FDA as a relabeler, or a repackager if limited repackaging will occur as permitted in this proposed rule, under section 510(b) of the FD&C Act, in accordance with part

207, and also list the drug as required. We note that an entity that is a “repackager” as defined in the DSCSA under section 581(16) of the FD&C Act is likely to already have facilities and capabilities in place to affix or imprint a product identifier based on existing DSCSA requirements. A relabeler who contracts with the Importer to affix a product identifier on the Importer’s behalf must, even if not engaged in a repackaging operation with respect to the eligible prescription drug, have systems and processes in place to meet applicable requirements of a “repackager” under section 582(e) of the FD&C Act for any transaction involving the eligible prescription drug.

Per section 581(14) of the FD&C Act, the product identifier must include a standardized numerical identifier (SNI), as that term is defined in section 581(20) of the FD&C Act, the lot number, and expiration date of the product and be in human and machine-readable form encoded in a 2-dimensional barcode. An SNI consists of an alphanumeric serial number and NDC under section 581(20). For a product imported under section 804 of the FD&C Act, the Importer is responsible for obtaining an NDC for the product (as described elsewhere in this proposed rule). With regard to the serial number component of the SNI, the Importer may elect to use the same serial number (i.e., the SSI) that the Foreign Seller had previously assigned to the product, or it may elect to assign a new serial number. Under the proposed rule, the Importer would need to maintain records, for no less than 6 years, that allow the Importer to associate the product identifier it affixed on each package and homogenous case of product it received from the Foreign Seller, with the SSI that had been assigned by the Foreign Seller, and the Canadian DIN that was on the package when the Foreign Seller received the product from the original manufacturer. This is analogous to the record retention requirement in section 582(e)(2)(A)(iv)

of the FD&C Act for a repackager that associates a product identifier with a manufacturer-affixed product identifier.

In addition to the requirements proposed in the rule, the Importer is required to comply with any applicable existing requirement of the DSCSA for subsequent transactions to trading partners in the supply chain once the product has been relabeled with the required U.S. labeling (including the product identifier). For example, any Importer of eligible drugs under a SIP who is a “pharmacist” as defined in section 804(a)(2) of the FD&C Act (i.e., a person licensed by a State to practice pharmacy, including the dispensing and selling of prescription drugs), is also considered to be a “dispenser” under the DSCSA, as defined in section 581(3) of the FD&C Act. Such dispenser must be “authorized” under the DSCSA, i.e., have a valid license under State law (as defined in section 581(2)(D) of the FD&C Act). Such dispenser must also comply with all applicable requirements pertaining to a dispenser under section 582(d) of the FD&C Act. Furthermore, any Importer of eligible drugs under section 804 who is a “wholesaler” as defined in section 804(a)(5)(A) of the FD&C Act, is also considered to be a “wholesale distributor” under the DSCSA, as defined in section 581(29) of the FD&C Act. Such wholesale distributor must be “authorized” under the DSCSA, i.e., have a valid license under State law or section 583, in accordance with section 582(a)(6) of the FD&C Act, and otherwise meet the definition in section 581(2)(C) of the FD&C Act. Such wholesale distributor must also comply with all applicable requirements pertaining to a wholesale distributor under section 582(c) of the FD&C Act.

3. Exemptions from Certain DSCSA Requirements

We propose to exempt certain transactions from DSCSA requirements in section 582 of the FD&C Act, as permitted by section 582(a)(3)(iii), because they would be difficult or

impossible for section 804 imported drugs to meet, and the proposed rule includes other safeguards to maintain supply chain security:

- *Section 582(c)(1)(A) and (d)(1)(A)*: For an Importer that is a wholesale distributor receiving the product from a Foreign Seller in Canada, the proposed rule would exempt the Importer from the requirement not to accept ownership unless the previous owner provides the transaction history, transaction information, and a transaction statement for the product. Similarly, if the Importer is a pharmacist receiving the product from a Foreign Seller in Canada, the proposed rule would exempt the Importer from the requirement on dispensers to not accept ownership unless the previous owner provides the transaction history, transaction information, and a transaction statement for the product. Instead, as previously described, this rule proposes to require the Foreign Seller to provide certain transaction-related information to the Importer that is adequate to ensure no additional risk to supply chain security.
- *Section 582(c)(2) and (d)(2)*: The proposed rule would exempt Importers that are wholesale distributors and dispensers from the prohibition on receiving products that are not encoded with a product identifier. Instead, as previously described, products received from the Foreign Seller would be required to have an SSI. Wholesale distributors and dispensers would otherwise be required to engage only in transactions of products encoded with a product identifier, as defined in DSCSA.
- *Section 582(c)(3) and (d)(3)*: Importers that are wholesale distributors and dispensers would be permitted to conduct transactions with Foreign Sellers even though they are not “authorized trading partners” under section 581. Wholesale distributors and dispensers

would otherwise be required to transact only with authorized trading partners, as defined in the DSCSA.

- *Section 582(c)(4)(A)(i)(II) and (d)(4)(A)(ii)(II)*: For section 804 imported products, the proposed rule would exempt an Importer from the requirement to verify that a product in the Importer’s possession or control contains a “standardized numerical identifier.” Instead, the Importer would be required to verify that the section 804 imported product at the package level includes the SSI that the Foreign Seller had previously assigned to the product.

Note that FDA would not consider a drug imported under section 804 to have been diverted solely as a result of being imported under a SIP. A drug imported under section 804 may meet the definition of suspect or illegitimate product for other reasons, however (e.g., counterfeit or stolen products), and entities that are obligated to identify such products under the DSCSA would be obligated to do so for drugs imported under section 804 in the same manner as they would for any other drugs subject to the same requirement.

We welcome comments on whether FDA should include exemptions from additional DSCSA requirements. We also note that manufacturers, repackagers, wholesale distributors, or dispensers may request waivers or exceptions at any time, under section 582(a)(3)(i) and (ii) of the FD&C Act.

4. Manufacturer’s Supply Chain Security Obligations

Pursuant to section 804(d)(1) of the FD&C Act, this regulation, once finalized, would require the Importer to submit to FDA certain information and records about the imported drug. Under section 804(d)(1)(J) of the FD&C Act, such information would include the results of testing for authenticity and degradation, to be done per section 804(e) by either the Importer or

the manufacturer. In the case of testing that is done by the Importer, other parts of this regulation specify information that the manufacturer is required to share in confidence with the Importer in order for the testing to occur, but in this section we further propose that the manufacturer would also need to provide to the Importer information it has about the transaction of the drug to the Foreign Seller located in Canada. Such information is necessary, along with other testing and laboratory record information specified elsewhere in this proposed rule, to ensure that the imported drug is authentic, as required in section 804(d)(1)(J) of the FD&C Act. Furthermore, under section 804(d)(1)(N) of the FD&C Act, we consider such information pertaining to drug's transactions in the pre-U.S. supply chain to be necessary to ensure the protection of public health.

Manufacturers would also need to be able to provide sufficient information to the Importer about the imported drug's movements in the pre-U.S. supply chain. To this end, this rule proposes to require, under section 804(e) of the FD&C Act, that the manufacturer provide to the Importer all relevant documentation about the transaction that it provided to the Foreign Seller, upon its transfer of ownership of the product for the Canadian market. The rule does not propose to require any additional information about this transaction that is otherwise not maintained or submitted in accordance with Canadian law, or in the normal course of business for products the manufacturer intends to introduce to the Canadian market. The Importer would be required to use this information obtained from manufacturers under section 804(e) of the FD&C Act to help determine whether the supply chain was intact, by comparing the information about the transaction between the manufacturer and Foreign Seller to that received by the Importer from the Foreign Seller, as required under this rule.

We seek comments on this approach, including whether different or additional safeguards are necessary to ensure the integrity of the supply chain with respect to drugs imported under section 804 of the FD&C Act.

G. Requirements for Qualifying Laboratories

Section 804 of the FD&C Act requires that imported drugs be tested by a “qualifying laboratory,” which is defined as “a laboratory in the United States that has been approved by the Secretary for the purposes of this section.” As indicated earlier in this document, a SIP Proposal would need to indicate which laboratory the SIP will use to test the drugs it imports. The SIP Proposal would also need to explain why that laboratory is qualified to do the testing and so should be approved by FDA for use by a SIP.

To be considered qualified, we propose that a laboratory would need to comply with the applicable elements of the CGMP requirements, including provisions regarding laboratory controls in 21 CFR 211.160 and regarding laboratory records in 21 CFR 211.194. In addition, a laboratory would need to have ISO 17025 accreditation. Finally, we propose that it also would need to have an FDA inspection history and it would need to have satisfactorily addressed any objectionable conditions or practices identified during its most recent FDA inspection.

We seek comment on whether there are other requirements that all laboratories should meet before FDA approves them for use by a SIP. For example, we seek comment on whether we should require accreditation different from or in addition to ISO 17025.

If the rule is finalized as proposed, FDA would approve qualifying laboratories for use by a SIP on a case-by-case basis as part of its review and authorization of a SIP Proposal. FDA would also consider publishing a list of approved qualifying laboratories for the benefit of States

or other non-federal governmental entities and their co-sponsors, if any, that may be developing a SIP Proposal.

H. Laboratory Testing Requirements

Section 804(d)(1)(J)(i) of the FD&C Act sets forth testing requirements for shipments of imported drugs that are shipped directly to the Importer from the first foreign recipient of the prescription drug from the manufacturer and section 804(d)(1)(J)(ii) sets forth testing requirements for shipments that are not shipped directly to the Importer from the first foreign recipient of the prescription drug from the manufacturer. Because we are proposing to require that all shipments under a SIP be shipped directly from the Foreign Seller, which is the first foreign recipient of the prescription drug from the manufacturer, to the Importer, this rule focuses on the testing requirements in section 804(d)(1)(J)(i) and does not address the requirements in section 804(d)(1)(J)(ii) of the FD&C Act. In addition, section 804(d)(1)(L) of the FD&C Act requires that the Importer provide laboratory records to FDA that include “complete data derived from all tests necessary to ensure that the prescription drug is in compliance with established specifications and standards.”

Section 804(d)(1)(J)(i) of the FD&C Act provides that, in the case of an initial imported shipment, an Importer must provide documentation to FDA demonstrating that the drug “was received by the recipient from the manufacturer and subsequently shipped by the first foreign recipient to the importer,” that “the quantity being imported into the United States is not more than the quantity that was received by the first foreign recipient,” and that “each batch of the prescription drug in the shipment was statistically sampled and tested for authenticity and degradation.” For any subsequent shipments from the same batch of a drug, section 804(d)(1)(J)(i)(III)(bb) of the FD&C Act allows for more limited testing, of “a statistically valid

sample of the shipment.” For an initial imported shipment, the testing would have to be done on a statistical sample of “each batch of the prescription drug in the shipment.” For example, if a shipment contained drugs from two batches, Batch A and Batch B, the testing would have to be done on a statistical sample of all of the drugs that came from Batch A and on a separate statistical sample of all the drugs that came from Batch B. For a subsequent shipment, the testing could be done on a statistical sample of the shipment as a whole, unless, for example, there are drugs from a third batch, Batch C, in the shipment. In that case, the testing would need to be done on a statistical sample of all the drugs that came from Batch A and Batch B, as a whole, and on a separate statistical sample of all the drugs that came from Batch C.

We propose to require that a statistical sample of a batch or shipment of section 804 drugs be randomly selected from the batch or shipment being tested or, in the alternative, that the sample be representative of the batch or shipment. We seek comment on whether we should specify a sampling method. We also seek comment on whether we should require that sampling be done according to an established standard such as those issued by the American National Standards Institute (ANSI) or by ASTM International.

Regarding the size of the sample, the number of packaged units in the sample would need to be large enough to enable a statistically valid statement to be made regarding the authenticity and stability of the entire batch or entire shipment. We seek comment on whether we should require that the sample size be determined using an established standard such as ASTM International’s E122-17 “Standard Practice for Calculating Sample Size to Estimate, With Specified Precision, the Average for a Characteristic of a Lot or Process” (Ref. 30).

As noted previously, we propose that the testing done on the sample of the batch or shipment be sufficiently thorough to establish, in conjunction with data and information from the

manufacturer, that the batch or shipment is eligible for importation under a SIP. The proposed rule would require the sample of the HPFB-approved drug to be tested to confirm that the HPFB-approved drug meets the FDA-approved drug's specifications, including the analytical procedures and methods and the acceptance criteria. In addition, to meet the statutory requirement that shipments be tested for degradation, a stability-indicating assay provided by the manufacturer would be required to be conducted on the sample of the drug that is proposed for import. Pursuant to section 804, the proposed rule would require all testing to be done in a qualifying laboratory in the United States.

The testing required under section 804(d)(1)(J) of the FD&C Act can be conducted "by the importer or by the manufacturer." If the Importer conducts the testing, section 804(e)(2)(A) of the FD&C Act requires the manufacturer to provide the Importer with the information needed to authenticate the prescription drug. Under the proposed rule, specifically, the manufacturer would be required to provide the Importer with formulation information about the HPFB-approved drug and the FDA-approved drug and any testing methodologies and protocols that the manufacturer has developed that the Importer needs to conduct the Statutory Testing.

In addition, under the proposed rule, the manufacturer would be required to provide an attestation to the Importer, or alternatively to FDA if the manufacturer conducts the testing itself, to establish that, but for the fact that it bore the HPFB-approved labeling, the drug that the manufacturer sold to the Foreign Seller in fact met the conditions in the FDA-approved NDA or ANDA. This would include any process-related or other requirements for which compliance cannot be established through laboratory testing. If the manufacturer does the testing, the manufacturer would be required to provide the attestation to FDA under the proposed rule. We propose that the attestation would need to include confirmation that the HPFB-approved drug has

the active ingredient(s), active ingredient source(s) (including manufacturing facility or facilities), inactive ingredient(s), dosage form, strength(s), route(s) of administration, etc., described in the FDA-approved drug's NDA or ANDA. The attestation would also need to confirm that the HPFB-approved drug conforms to the specifications in the FDA-approved drug's NDA or ANDA regarding the quality of the drug substance(s), drug product, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of the drug. In addition, the attestation would need to confirm that the HPFB-approved drug was manufactured in accordance with the specifications described in the FDA-approved drug's NDA or ANDA, including with regard to the facilities and manufacturing lines that are used, and in compliance with CGMP requirements set forth in section 501(a)(2)(B) of the FD&C Act and 21 CFR parts 4 (if a combination product), 210, and 211. The attestation would also need to include the original date of manufacture or whatever date was used in calculating the labeled expiration date based on the HPFB-approved or scientifically validated expiration period, the expiration period set forth in the FDA-approved drug's NDA or ANDA, and any other information needed to label the drug with an expiration date that meets the specifications of the FDA-approved drug's NDA or ANDA.

The attestation would also need to include information needed to confirm that the labeling of the prescription drug complies with labeling requirements of the FD&C Act. Finally, as discussed elsewhere in this proposed rule, the attestation would need to include information about the transaction of the eligible prescription drug to the Foreign Seller.

In addition to the attestation, the manufacturer would need to provide the Importer with the executed batch record, including the executed COA, for at least one recently manufactured, commercial-scale batch of the HPFB-approved drug and for at least one recently manufactured

commercial-scale batch of the FDA-approved drug that was produced for and released for distribution to the U.S. market under an NDA or ANDA. The manufacturer would need to provide these analyses for each manufacturing line that the manufacturer used to produce either or both of the drugs.

As discussed earlier in this document, section 804(e)(2)(B) of the FD&C Act states that the information that a manufacturer provides to an Importer under section 804(e)(2)(A) must be kept in strict confidence and used only for purposes of testing or otherwise complying with this Act.” The statute goes on to state that the regulations implementing section 804 of the FD&C Act can include provisions to provide for the protection of trade secrets and commercial or financial information that is privileged or confidential. We have proposed in § 251.15(g) and (h) additional provisions regarding the protection of information that may be supplied by a manufacturer to an Importer under this rule. We seek comment on whether any other provisions are needed to protect the information that manufacturers would need to provide to Importers under this rule. We note that instead of providing its proprietary test methods to an Importer, a manufacturer can do the testing itself in a qualifying laboratory in the United States.

As discussed above, for subsequent shipments of drugs from a batch, drugs from which have already been imported under a SIP, section 804(d)(1)(J)(i)(III)(bb) of the FD&C Act allows Importers to test a statistically valid sample of each shipment, as opposed to a statistically valid sample of each batch within a shipment. We seek comment on whether a different approach to testing subsequent shipments should be permitted. For example, it may be appropriate to use vibrational spectroscopic tests to test drugs in subsequent shipments. We note, however, that formulation-related physical stability and other quality issues cannot be tested by using spectroscopy. For that reason, a stability-indicating assay developed by USP or the manufacturer

would have to be conducted as well. We seek comment on what testing would be appropriate at this stage.

The obligations on manufacturers under section 804(e) of the FD&C Act are enforceable under section 301(aa) of the FD&C Act, which provides that, among other things, a violation of the regulations implementing section 804 is a prohibited act. Furthermore, section 303(b)(6) of the FD&C Act sets forth penalties for manufacturers or Importers that knowingly fail to comply with a requirement of section 804(e) of the FD&C Act. These requirements include that: (1) the manufacturer or Importer conduct the Statutory Testing at a qualifying laboratory; (2) if the Importer conducts the testing, the manufacturer supply the information needed to authenticate the drug being tested and to confirm that the labeling is in compliance with the FD&C Act in a timely fashion, and (3) if the manufacturer supplies information to the Importer, the Importer keep it in strict confidence and only use it for testing and complying with the FD&C Act. A manufacturer or Importer that fails to comply with these requirements can be imprisoned for not more than 10 years under section 303(b)(6) of the FD&C Act, fined under 18 U.S.C.3571, or both.

In the event that a manufacturer fails to provide information required by this proposed rule in a timely fashion, including information necessary for the Importer to conduct the Statutory Testing, authenticate the drug being tested, or confirm that the labeling is in compliance with the FD&C Act, FDA may provide such information to an Importer if the information is contained in the manufacturer's approved NDA or ANDA. We seek comment on what would be considered a timely fashion that would provide the manufacturer adequate time to provide the necessary information and that would not create excessive difficulty for the Importer who needs that information to import the drugs.

I. Listing and Labeling of Eligible Prescription Drugs

Section 804(d)(1)(K)(ii) of the FD&C Act requires that a drug covered by section 804 meets all labeling requirements of the FD&C Act. Additionally, section 804(c) of the FD&C Act requires that each prescription drug imported under this importation program comply with sections 501, 502, and 505 of the FD&C Act. Under section 804(h) of the FD&C Act, the manufacturer of a prescription drug is required to provide the Importer with written authorization to use the drug's approved labeling at no cost. If the manufacturer fails to do so in a timely fashion, FDA will deem this authorization to have been given. In addition, under the proposed rule, as required by section 804(e)(2)(A)(ii) of the FD&C Act, the manufacturer would need to supply the Importer, in a timely fashion, with information needed to confirm that the labeling of the prescription drug complies with the labeling requirements of the FD&C Act. Furthermore, under the requirements proposed by this rule, before a drug can be introduced into interstate commerce under section 804 of the FD&C Act, it would be required to be listed in accordance with part 207, and it would be relabeled so that it bears certain information that is unique to the eligible prescription drug. Specifically, the labeling will need to display an NDC that is unique to the eligible prescription drug, and it will need to provide information about the Importer. This section describes the proposed requirements for obtaining an NDC, listing, and relabeling an eligible prescription drug.

The rule proposes that before an eligible prescription drug can be sold it would need to bear a new NDC and be listed. We note that drugs imported under section 804 will have the same name but will have a different NDC than do their FDA-approved counterparts. As stated above, the Importer of an eligible prescription drug would need to either: (1) propose an NDC for the drug, following the procedures in § 207.33, and it would need to list the drug, following

the procedures in § 207.53 or (2) if the Importer is a private label distributor, take responsibility to ensure that the entity performing relabeling on its behalf proposes an NDC and lists each eligible prescription drug in accordance with the applicable requirements of part 207.

Additionally, we propose to make the Importer responsible for relabeling the drug, or arranging for it to be relabeled, to meet the requirements of this proposed rule. The relabeling and associated limited repackaging activities must meet applicable requirements, including applicable CGMP requirements under parts 210 and 211. At the time that an eligible prescription drug is sold or dispensed it would need to have been relabeled to be consistent with the FDA-approved the carton and container labels, prescribing information, and any patient labeling, such as medication guides, instruction for use documents, and patient package inserts. In addition, the eligible prescription drug would need to have been assigned a product identifier in compliance with section 582 of the FD&C Act. The relabeled eligible prescription drug will be considered consistent if it varies from the FDA-approved carton and container labels, prescribing information, and patient labeling solely to the extent described in this rule.

Except for repackaging that is necessary to perform the relabeling described in this proposed rule, the proposed rule would not allow further repackaging of drugs imported pursuant to a SIP. “Repack” or “repackage” is defined in § 207.1 as “the act of taking a finished drug product or unfinished drug from the container in which it was placed in commercial distribution and placing it into a different container without manipulating, changing, or affecting the composition or formulation of the drug.” We believe that allowing repackaging that breaches the immediate container closure system introduces unnecessary risk of adulteration, degradation, and fraud for drugs subject to a SIP. We also note that some container closure systems include a tamper-evident seal, which would be disturbed if repackaging were allowed. In addition, if a

drug is repackaged from its immediate container closure, the expiration period set forth in the NDA or ANDA may no longer be valid because the expiration period in an approved NDA or ANDA is based on stability studies involving the particular container closure system into which a drug is placed without opening it to expose the contents to the outside environment. Additional stability studies would generally be required to establish a new expiration period.

The proposed rule would require that the prescribing information of an eligible prescription drug would need to include that drug's NDC in the HOW SUPPLIED/STORAGE AND HANDLING section for products with Physician Labeling Rule (PLR) labeling (see § 201.57(c)(17)(iii) (21 CFR 201.57(c)(17)(iii))) or the HOW SUPPLIED section for products with "old" (non-PLR) format labeling (see § 201.80(k)(3) (21 CFR 201.80(k)(3))) in place of any NDCs assigned to the FDA-approved U.S. versions of the drug. The proposed rule would also require that the eligible drug's new NDC be added to the container label and the carton labeling. If applicable, the new NDC would replace any NDC otherwise appearing on the label and carton labeling of the FDA-approved version of the drug. We seek comment on whether having multiple otherwise identical drugs in the marketplace with different NDCs will create any issues, such as with pharmacy dispensing or otherwise, and, if so, if there are steps that can be taken to mitigate such issues.

In addition to the names and places of businesses of entities that appear on the FDA-approved labeling, in this rule we propose to require that the label and labeling of an eligible prescription drug also bear conspicuously the name and place of business of the Importer. If the FDA-approved labeling does not include the name and place of business of the manufacturer, the name and place of business of the manufacturer should be added as well.

We also propose to require that the labeling on or within the package from which the drug is dispensed include the following statement: “This drug was imported from Canada under the [Name of State or Other Governmental Entity and of Its Co-Sponsors, If Any] Section 804 Importation Program to reduce its cost to the American consumer.” If the SIP maintains a website, the statement could also include the website address. To help avoid potential confusion between products with the same name, we propose that this statement would be included after the PATIENT COUNSELING INFORMATION section for products subject to § 201.56(d) (21 CFR 201.56(d)) and § 201.57, or after the HOW SUPPLIED section (or after the last section of labeling) for products subject to §§ 201.56(e) and 201.80. The statement also would be included on the immediate container and outside package to help pharmacists distinguish a section 804 product when selecting the product on the pharmacy shelf. The statement would be sufficiently prominent to help a pharmacist readily distinguish the eligible prescription drug without obscuring required or recommended information (e.g., information that will reduce the risk of medication errors and ensure safe administration of the drug) (see FDA, 2013, “Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.” Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>). The statement may also aid in pharmacovigilance by increasing the likelihood that adverse event, medication error, field alert, and other reports include the fact that the drug was imported under a SIP. We seek comments on the content of the disclosure statement, in particular whether such a statement is necessary, whether it will be understandable and meaningful to prescribers, pharmacists, and patients, and whether more or less information is

needed. We seek comment on whether it is necessary to provide the name of the SIP or whether it would be sufficient to state that the drug was imported under a SIP.

If an eligible prescription drug's container is too small to fit the additional information required by this proposed rule, FDA would consider a proposal for supplementary labeling from the SIP Sponsor. The container label would need to include at minimum the product's proprietary and established name (if any); product strength; lot number; and the name of the manufacturer and the Importer (see FDA, 2013, "Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors." Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>).

In addition to the required statement on the labeling, the proposed regulation also would require the SIP Sponsor to describe in the SIP Proposal how it will educate pharmacists, healthcare providers, and patients about its SIP. If pharmacists, healthcare providers, and patients know that a drug was originally intended for sale in Canada, they will have the ability to include this information if they subsequently report any adverse events or quality concerns. It may also help ensure that a recall is effective if healthcare providers and patients have this knowledge.

Among other things, a SIP could create and maintain a website that would set forth the name and NDC number of each drug that it imports. This would allow pharmacists, healthcare providers, and patients to use the NDC number to determine at any time whether a drug was originally intended for sale in Canada. The website could also include any relevant adverse event, medication error, field alert reports, or other reports or recall information. As stated

earlier, the website address could be included along with the disclosure statement in the labeling of an eligible prescription drug.

A SIP could also distribute a Dear Healthcare Provider letter to physicians and pharmacists by United States mail, by email, by posting the letter on the Importer's website, or by other effective means, explaining that the drugs will have a different NDC because they were originally intended for sale in Canada. The letter could recommend that patients be counseled that the drugs were originally intended for sale in Canada, that they have different NDCs than their FDA-approved counterparts, and that they can use the NDCs to find out pertinent new information regarding the HPFB-approved drug or its FDA-approved counterpart, including information about recalls. A SIP could also propose to distribute a Dear Consumer letter (similar to a Dear Healthcare Provider letter) that pharmacists could dispense along with eligible prescription drugs and that consumers could access on the SIP's website.

J. Information and Records

Section 804(d) of the FD&C Act lists information and documentation, to be required in the regulations under section 804(b), that Importers of eligible prescription drugs must submit to the Secretary. The rule proposes that section 804(d) information would be submitted to FDA each quarter by SIP Sponsors. SIP Sponsors would be required to submit a report to FDA each quarter containing the information set forth in section 804(d) of the FD&C Act, beginning after the SIP Sponsor files an electronic import entry for consumption for its first shipment of drugs.

Consistent with the statute, the proposed rule would require that Importers collect and submit to FDA the information listed here, but also clarifies that the Importer's submission obligations are met if the SIP sponsor submits a report to FDA as described above: (1) the name, address, telephone number, and professional license number (if any) of the Importer; (2) the name and quantity of the active ingredient of the prescription drug; (3) a description of the

dosage form of the prescription drug; (4) the date on which the prescription drug is shipped; (5) the quantity of the prescription drug that is shipped; (6) the lot or control number assigned to the prescription drug by the manufacturer of the prescription drug; (7) the point of origin and destination of the prescription drug; and (8) the per unit price paid by the Importer for the prescription drug in U.S. dollars, as well as any other information that FDA determines is necessary to ensure the protection of the public health. We propose to require that Importers submit to FDA, in addition to the point of origin (i.e., the manufacturer of the finished dosage form) and the destination (i.e., the wholesaler, pharmacy, or patient to whom the Importer sells or dispenses the drug), information regarding the rest of the supply chain, which this rule proposes would consist solely of the Foreign Seller in Canada.

Section 804(d) of the FD&C Act also requires the Importer to collect and submit to FDA certain documentation, including: (1) documentation from the Foreign Seller specifying the original source of the prescription drug (which under this rule would be the manufacturer of the eligible prescription drug) and the quantity of each lot of the prescription drug originally received by the seller from that source and (2) in the case of a prescription drug that is shipped directly from the first foreign recipient of the prescription drug from the manufacturer (which, under this rule, would be the Foreign Seller), documentation demonstrating that the prescription drug was received by the first foreign recipient from the manufacturer and subsequently shipped by the first foreign recipient to the Importer. The Importer must also collect and submit documentation of the quantity of each lot of the prescription drug received by the first foreign recipient demonstrating that the quantity being imported into the United States is not more than the quantity that was received by the first foreign recipient. While the Importer does not need to submit records associating the eligible prescription drugs' SSIs with their U.S. product

identifiers, the Importer would need to maintain such records and make them available to FDA upon request. In the case of an initial imported shipment, Importers would also need to submit documentation demonstrating that each batch of the prescription drug in the shipment was statistically sampled and tested for authenticity and degradation, and in the case of any subsequent shipment, they would need to submit documentation demonstrating that a statistically valid sample of the shipment was tested for authenticity and degradation.

Importers also would need to submit a certification from the Importer or the manufacturer of an imported drug that the drug is approved for marketing in the United States and is not adulterated or misbranded, and meets all labeling requirements under the FD&C Act. In this rule, we propose to require that the certification include: (1) that there is an approved SIP; (2) that the drug is covered by the SIP; (3) that the drug is an eligible prescription drug as defined in this rule; (4) that the FDA-approved counterpart of the drug is currently commercially marketed in the United States; (5) that the drug is approved for marketing in Canada; and (6) that the drug is not adulterated or misbranded and meets all labeling requirements under the FD&C Act. Importers would need to collect and submit laboratory records, including complete data derived from all tests necessary to ensure that the prescription drug is in compliance with established specifications and standards, and documentation demonstrating that the Statutory Testing was conducted at a qualifying laboratory, unless the manufacturer conducted the Statutory Testing and submitted the relevant information directly to FDA.

In addition, SIP Sponsors would be required to provide FDA with data and information on the SIP's cost savings to the American consumer. We recognize a SIP's scope will influence the appropriate cost savings calculation methodology. SIPs should, therefore, report their total cost savings to consumers as well as the methodology used to calculate this measure. Cost

savings calculations should be based on savings to the American consumer. Calculations should therefore rely, to the greatest extent possible, on prices paid by the intended consumer population. Average price measures by drug may be appropriate if drugs are dispensed through multiple channels or if the imported drugs' prices fluctuate throughout the reporting period. Calculation methods should also account for factors that may influence cost savings over time, such as changes in drug utilization, the price of domestic drugs, and exchange rates. As mentioned above, we anticipate that some SIP Sponsors may seek to import drugs to be used by patients in State-run programs. In such cases, a SIP Sponsor could submit information about whether cost-sharing expenses are reduced for the participants, or whether the program will result in cost savings that are passed on to consumers in other ways, such as increasing the number of people who can be covered by a State program, or increasing the availability of drugs covered by the program. We seek comments on these and other factors relevant to the reporting of cost savings.

K. Post-Importation Requirements

Under proposed § 251.18, SIP Sponsors and Importers would be required to take certain actions regarding eligible prescription drugs if they are violative of an applicable requirement. Under the proposed rule, the SIP Sponsor would be required to immediately stop importation of eligible prescription drugs under a SIP if it determines that a drug or entity in the supply chain does not meet all applicable requirements of the FD&C Act, FDA regulations, and the authorized SIP. The Importer must establish and maintain records and submit reports to FDA and to the manufacturer of all domestic adverse events and medication errors associated with the use of their imported eligible prescription drugs about which they obtain or otherwise receive information. These reports would be required to help inform whether there are safety concerns

with imported eligible prescription drugs, generally, and also specifically in relation to the handling of these drugs. The Importer must also develop written procedures for the surveillance, receipt, evaluation, and reporting of adverse events and medication errors to FDA and to the relevant manufacturer.

The Importer must submit expedited reports on adverse events that are both serious and unexpected to FDA and the manufacturer as soon as possible but no later than 15 calendar days from initial receipt of the information by the Importer. The Importer must also submit expedited reports on medication errors to FDA and the manufacturer within the same timeframe.

The Importer must promptly investigate all adverse events and medication errors that are the subject of these expedited reports and must submit follow-up reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, the Importer should maintain records of the unsuccessful steps taken to seek additional information. Furthermore, the Importer must submit reports on adverse events that are both serious and expected or that are nonserious, whether expected or unexpected, to FDA and the manufacturer within a 90-calendar day timeline.

FDA may require the Importer to submit certain adverse events within 15 calendar days, even though the events do not meet the criteria for expedited reporting. FDA will specify these adverse events in advance and will provide the reason for requiring that they be reported to the Agency on an expedited basis.

While § 314.80(c)(1)(iii) (21 CFR 314.80(c)(1)(iii)) gives distributors of approved drugs the choice of submitting reports to either FDA or the applicant, we propose to require that Importers of section 804 drugs be required to submit reports to both FDA and the manufacturer. This will aid the manufacturer in its pharmacovigilance efforts, and it will provide FDA with

information that may be relevant to its review of SIP Proposals and Pre-Import Requests as well as to its oversight of drugs imported under section 804 of the FD&C Act and section 804 in general.

FDA proposes to require submission of individual case safety reports (ICSRs) and ICSR attachments in electronic format, as described in § 314.80(g)(1). Importers may request in writing a temporary waiver of the electronic reporting requirements as described in § 314.80(g)(2). Such waivers will be granted on a limited basis and for good cause.

The Importer would also be required to submit to the manufacturer and to FDA field alert reports about the products it distributes. These reports would need to be made when the Importer becomes aware of information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article, or information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the FDA-approved NDA or ANDA. If a SIP imports a drug-device combination product, the Importer would also need to submit to the manufacturer and to FDA the reports described in 21 CFR 4.102(c)(1) for combination products containing a device constituent part, in the manner and by the deadlines provided in part 4. The Importer would also need to maintain the records described in 21 CFR 4.102(c)(1) and 4.105(b).

An Importer should notify the Foreign Seller and the SIP Sponsor any time it makes an adverse event, medication error, field alert report, or other report to FDA and the manufacturer. Notification to Health Canada would be done by the Foreign Seller in accordance with Health

Canada requirements. FDA would share adverse event, medication error, field alert report, or other report information it receives with Health Canada as appropriate.

The SIP Sponsor would be required to establish a procedure to track the public announcements of the manufacturer of each of the drugs that they import and they must also monitor FDA's recall website at <https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts>, and Health Canada's recall website at <https://healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php?cat=3>, for any recall or market withdrawal information relevant to the drugs that they import under section 804 of the FD&C Act. The SIP Sponsor would have to explain in its SIP Proposal how it will ensure that information about recalls or market withdrawals will be shared among the SIP Sponsor, the Foreign Seller, the Importer, and FDA and provided to the manufacturer.

If FDA or a SIP Sponsor determines that a recall is necessary, the SIP Sponsor must ensure that the recall is carried out effectively based on the classification and depth determined by FDA or the SIP Sponsor. A SIP must have a written recall plan that describes the procedures to perform a recall of the product and specifies who will be responsible for performing the procedures. The recall plan must cover recalls initiated by FDA and recalls initiated by the SIP Sponsor, as well as recalls in Canada or the United States initiated by a drug's manufacturer that implicate a drug imported under a SIP, with which the Foreign Seller and/or Importer must cooperate. The recall plan must include sufficient procedures for the SIP Sponsor, Foreign Seller and/or Importer to:

- immediately cease distribution of the drugs affected by the recall;
- directly notify consignees of the drug or drugs included in the recall, including how to return or dispose of the recalled drugs;

- specify the depth to which the recall will extend (e.g., wholesale, intermediate wholesale, retail, or consumer level);
- notify the public about any hazard or hazards presented by the recalled drug when appropriate to protect the public health;
- conduct effectiveness checks to verify that all consignees at the specified recall depth have received notification about the recall and have taken appropriate action;
- appropriately dispose of recalled product; and
- notify FDA of the recall.

In addition, in the event of a recall, Importers and Foreign Sellers would be required, upon request by FDA, to provide the transaction history, information, and statement, as those terms are defined in sections 581(25), 581(26), and 581(27) of the FD&C Act, respectively, of the FD&C Act. We seek comment on how a SIP Sponsor and co-sponsor, if any, Foreign Seller, or Importer would effectuate a recall in the United States, given that this will be a new responsibility for these entities.

L. Severability

Proposed § 251.20 contains a severability provision clarifying the Agency's intent regarding whether the provisions of part 251 are severable from the rest of the regulation if one or more of the provisions are stayed or determined to be invalid by a court. The provisions of part 251 contain requirements that are either expressly mandated by section 804 of the FD&C Act, or are otherwise necessary pursuant to section 804(c)(3) because they have been determined by the Secretary to be appropriate as a safeguard to protect the public health or as a means to facilitate the importation of prescription drugs under section 804. Each of the requirements that will be included in the final rule will address significant potential safety concerns associated with

drugs imported under section 804 and would be necessary to protect public health. If one or more of these provisions becomes invalid, the rule, as a whole, would no longer adequately protect public health and therefore should be invalid in its entirety.

In addition, section 804 of the FD&C Act, and by extension, this regulation, which is promulgated in part pursuant to that authority, only becomes effective if the Secretary certifies to Congress that implementation of section 804 will pose no additional risk to the public's health and safety. This certification is contingent upon this rule becoming effective with all the requirements that are included when finalized. If one or more of the provisions in this rule becomes invalid, in addition to the entire rule becoming invalid, the certification would become null and void because the certification is based on a finding that implementation of section 804 will pose no additional risk to the public's health and safety, and that finding would no longer be accurate because it would have been based on a final rule that contains all the requirements that were included when published.

VI. Proposed Effective and/or Compliance Dates

FDA proposes that any final rule that issues based on this proposal become effective 30 days after the final rule publishes in the *Federal Register*.

VII. Preliminary Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us 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). Executive Order 13771 requires that the costs associated with significant new regulations “shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations.” We believe that this proposed rule is a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. We cannot anticipate if sponsors will contract with small entities to implement their authorized SIP proposals and request comment on the impact the proposed rule may have on small entities. We also lack information to quantify the total impacts of the proposed rule. Therefore, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to 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 \$154 million, using the most current (2018) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

1. Summary of Costs and Benefits

The proposed rule, if finalized, would allow commercial importation of certain prescription drugs from Canada through time-limited programs, SIPs, sponsored by at least one non-federal governmental entity with possible co-sponsorship by a wholesaler or pharmacist. If

such programs allow Importers to leverage drug price differences between the United States and Canada, they will result in cost savings for U.S. consumers.

Expected costs of the proposed rule accrue to the Federal Government, SIP Sponsors, Importers, and manufacturers of imported drugs. The Federal Government would incur one-time fixed costs as well as ongoing costs to implement the rule, if finalized, and to review SIP Proposals and reports. SIP Sponsors would face costs to prepare proposals, implement approved SIPs, and produce SIP reports and records. SIPs may offer cost savings to consumers, as well as other parties in the drug supply chain including participating wholesale drug distributors, pharmacies, hospitals, and third-party payers. If their drugs are imported into the United States from Canada, drug manufacturers will have to provide importers with certain information. As drug distributors realize savings in acquiring imported drugs and pass some of these savings to consumers, it is possible that U.S. drug manufacturers may experience a transfer in U.S. sales revenues to these parties.

We are unable to estimate the cost savings from this proposed rule, as we lack information about the likely size and scope of SIP programs and about the specific drug products that may become eligible for importation, the degree to which imported drugs would be less expensive than non-imported drugs available in the United States, and which SIP eligible products are produced by U.S. drug manufacturers.

Table 1 summarizes the benefits and costs of the proposed rule.

Table 1.--Summary of Benefits, Costs and Distributional Effects of Proposed Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized \$millions/year				2019	7%	10	
					2019	3%	10	
	Annualized Quantified				2019	7%	10	
					2019	3%	10	
	Qualitative	Potential cost savings to consumers and third-party payers or entities					10	
Costs	Annualized Monetized \$millions/year				2019	7%	10	
					2019	3%	10	
	Annualized Quantified				2019	7%	10	
					2019	3%	10	
	Qualitative	Potential costs to Federal Government, SIP sponsors, importers, and manufacturers of imported drugs					10	
Transfers	Federal Annualized Monetized \$millions/year				2019	7%	10	
					2019	3%	10	
	From/ To	From:			To:			
	Other Annualized Monetized \$millions/year				2019	7%	10	
					2019	3%	10	
From/To	From: U.S. drug manufacturers			To: Importers and U.S. consumers			Not Quantified	
Effects	State, Local or Tribal Government: Potential costs and cost savings to State, tribal, and territorial government entities from sponsoring SIPs Small Business: Wages: Growth:							

We lack information about the likely size and scope of SIP programs, the specific drug products that may become eligible for importation, the degree to which drugs imported under section 804 would be less expensive than drugs not imported under section 804, and which SIP eligible products are produced by U.S. drug manufacturers to estimate the present and annualized values of the costs and cost savings of the proposed rule over an infinite time horizon. The designation under Executive Order 13771 of any final rule resulting from this proposal will be

informed by comments received and subsequent analysis at the final rule stage. Thus, we exclude the Executive Order 13771 summary table from this analysis.

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 31) and at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) and 25.31(a) 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.

IX. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). A description of these provisions is given below under the *Description* heading with an estimate of the annual reporting, recordkeeping, and third-party disclosure 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.

FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions

used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Section 804 Importation Program Proposals--21 CFR part 251

Description: The proposed regulations provide that a SIP Sponsor that seeks to implement a SIP to import prescription drugs from Canada must submit a proposal that includes, among other things, information about the SIP Sponsor and the SIP Sponsor's importation plan. In addition, SIP Sponsors must provide FDA with data and information on the drugs the SIP imports and on the SIP's cost savings to the American consumer. Importers would have a number of responsibilities related to submitting a Pre-Import Request, screening eligible prescription drugs and arranging for importation, testing, and relabeling. Manufacturers would provide information needed to authenticate eligible prescription drugs.

Description of Respondents: Respondents would include SIP Sponsors (State, tribal, or territorial governmental entities), Importers (pharmacists or wholesalers), and manufacturers of eligible prescription drugs.

FDA anticipates submissions will be made through the Electronic Submissions Gateway.

FDA estimates that there will be 10 SIP Sponsors requiring 360 hours each to research, prepare, and administer requirements annually; 10 Pre-Import Requests requiring 24 hours each annually; and 20 manufacturers also requiring 24 hours each annually to participate in the program. In addition, FDA estimates that a recordkeeping burden of 52 hours will be imposed annually on the 10 SIP Sponsors; and a recordkeeping burden of 24 hours will be imposed annually on each of the 10 Importers and the 20 manufacturers. The 20 manufacturers

anticipated to participate in the program will also incur an estimated burden of 24 hours each for copying and providing records to SIP Sponsors and Importers of foreign transactions.

FDA estimates the burden of this collection of information as follows:

Table 2.--Estimated Annual Reporting Burden¹

Type of Information Collection Activity/Respondent	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
SIP Sponsor 251.3; 251.8; 251.14--SIP Proposal Submission Requirements; 251.18--Post- Importation Requirements; 251.19--Reports to FDA	10	1	10	360	3,600
Importer 251.5; 251.12; 251.13; 251.17--Pre- Import Request and Importation Requirements	10	1	10	24	240
Manufacturer 251.16 Lab Testing Requirements	20	1	20	24	480
Total					4,320

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

Table 3.--Estimated Annual Recordkeeping Burden¹

Type of Information Collection Activity/Respondent	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
SIP sponsor 251.8--Modification or Extension of Authorized Importation Programs	10	1	10	52	520

Table 3.--Estimated Annual Recordkeeping Burden¹

Importer 251.14(d)--Supply Chain Security Requirements; 251.17--Importation Requirements; 251.18 Post- Importation Requirements	10	1	10	24	240
Manufacturer 251.14(b)--Supply Chain Security Requirements	20	1	20	24	480
Total					1,240

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

Table 4.--Estimated Annual Third-Party Disclosure Burden¹

Type of Information Collection Activity/Respondent	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
Manufacturer 251.14(b)--Supply Chain Security Requirements	20	1	20	24	480

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

To ensure that comments on information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB (see ADDRESSES). All comments should be identified with the title of the information collection.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3407(d)), we have submitted the information collection provisions of this proposed rule to OMB for review. These information collection requirements will not be effective until FDA publishes a final rule, OMB approves the information collection requirements, and the rule goes into effect. FDA will announce OMB approval of these requirements in the *Federal Register*.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed 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, we conclude 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.

XI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

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List of Subjects

21 CFR Part 1

Cosmetics, Drugs, Exports, Food labeling, Imports, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 251

Exports, Labeling, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, the Food and Drug Administration proposes to amend 21 CFR chapter I as follows:

PART 1--GENERAL ENFORCEMENT REGULATIONS

1. The authority citation for part 1 continues to read as follow:

Authority: 15 U.S.C. 1333, 1453, 1454, 1455, 4402; 19 U.S.C. 1490, 1491; 21 U.S.C. 321, 331, 332, 333, 334, 335a, 342, 343, 350c, 350d, 350e, 350j, 350k, 352, 355, 360b, 360ccc, 360ccc-1, 360ccc-2, 362, 371, 373, 374, 379j-31, 381, 382, 384a, 384b, 384d, 387, 387a, 387c, 393; 42 U.S.C. 216, 241, 243, 262, 264, 271; Pub. L. 107-188, 116 Stat. 594, 668-69; Pub. L. 111-353, 124 Stat. 3885, 3889.

2. Revise § 1.74 to read as follows:

§ 1.74 Human drugs.

In addition to the data required to be submitted in § 1.72, an ACE filer must submit the following information at the time of filing entry in ACE for drugs, including biological products

and eligible prescription drugs as defined in § 251.2 of this chapter that are imported or offered for import under section 804 of the Federal Food, Drug, and Cosmetic Act, intended for human use that are regulated by the FDA Center for Drug Evaluation and Research.

(a) For a drug intended for human use that is not an eligible prescription drug covered under paragraph (b) of this section:

(1) *Registration and listing.* The Drug Registration Number and the Drug Listing Number if the foreign establishment where the human drug was manufactured, prepared, propagated, compounded, or processed before being imported or offered for import into the United States is required to register and list the drug under part 207 of this chapter. For the purposes of this section, the Drug Registration Number that must be submitted at the time of entry in ACE is the unique facility identifier of the foreign establishment where the human drug was manufactured, prepared, propagated, compounded, or processed before being imported or offered for import into the United States. The unique facility identifier is the identifier submitted by a registrant in accordance with the system specified under section 510(b) of the Federal Food, Drug, and Cosmetic Act. For the purposes of this section, the Drug Listing Number is the National Drug Code number of the human drug article being imported or offered for import.

(2) *Drug application number.* For a drug intended for human use that is the subject of an approved application under section 505(b) or 505(j) of the Federal Food, Drug, and Cosmetic Act, the number of the new drug application or abbreviated new drug application. For a biological product regulated by the FDA Center for Drug Evaluation and Research that is required to have an approved new drug application or an approved biologics license application, the number of the applicable application.

(3) *Investigational new drug application number.* For a drug intended for human use that is the subject of an investigational new drug application under section 505(i) of the Federal Food, Drug, and Cosmetic Act, the number of the investigational new drug application.

(b) For an eligible prescription drug as defined in § 251.2 of this chapter that is imported or offered for import under section 804 of the Federal Food, Drug, and Cosmetic Act:

(1) *Registration and listing.* The Drug Registration Number and the Drug Listing Number. For the purposes of this section, the Drug Registration Number that must be submitted in ACE is the unique facility identifier of the Foreign Seller. The unique facility identifier is the identifier submitted by a Foreign Seller registrant under § 251.5 of this chapter. For the purposes of this section, the Drug Listing Number is the National Drug Code that the Importer will use when relabeling the eligible prescription drug as required in § 251.13 of this chapter.

(2) *Drug application number.* The number of the new drug application or abbreviated new drug application for the corresponding FDA-approved drug.

(3) *Lot or control number.* The lot or control number assigned by the manufacturer of the eligible prescription drug.

(4) *FDA Quantity.* FDA Quantity, which is the quantity of each eligible prescription drug in an import line delineated by packaging level, including the type of package from the largest packaging unit to the smallest packaging unit; the quantity of each packaging unit; and the volume and/or weight of each of the smallest of the packaging units.

(5) *Pre-Import Request number.* The Pre-Import Request number assigned by FDA.

3. Add part 251 to read as follows:

PART 251--SECTION 804 IMPORTATION PROGRAM PROPOSAL

Subpart A--General Provisions

Sec.

251.1 Scope of the part.

251.2 Definitions.

Subpart B--Section 804 Importation Program Proposals and Pre-Import Requests

251.3 SIP proposal submission requirements.

251.4 Review and authorization of importation program proposals.

251.5 Pre-Import Request.

251.6 Limitations on authorized importation programs.

251.7 Suspension and revocation of authorized importation programs.

251.8 Modification or extension of authorized importation programs.

Subpart C--Certain Requirements for Section 804 Importation Programs

251.9 Registration of Foreign Sellers.

251.10 Reviewing and updating registration information for Foreign Sellers.

251.11 Official contact and U.S. agent for Foreign Sellers.

251.12 Importer responsibilities.

251.13 Labeling of eligible prescription drugs.

251.14 Supply chain security requirements for eligible prescription drugs.

251.15 Qualifying laboratory requirements.

251.16 Laboratory testing requirements.

251.17 Importation requirements.

251.18 Post-importation requirements.

251.19 Reports to FDA.

251.20 Severability.

251.21 Consequences for violations.

Authority: 21 U.S.C. 351, 352, 353, 355, 371, 374, 381, 384.

Subpart A--General Provisions

§ 251.1 Scope of the part.

(a) This part sets forth the procedures that Section 804 Importation Program sponsors (SIP Sponsors) must follow when submitting plans to implement time-limited programs to begin importation of drugs from Canada under section 804 of the Federal Food, Drug, and Cosmetic Act. This part also sets forth certain requirements that are necessary for such programs to be authorized by FDA. Additionally, this part sets forth requirements for eligible prescription drugs and requirements for entities that engage in importation of eligible prescription drugs.

(b) This part includes provisions that exempt eligible prescription drugs that meet certain requirements from section 502(f)(1) of the Federal Food, Drug, and Cosmetic Act. It also includes provisions that exempt certain transactions involving eligible prescription drugs from certain requirements in section 582 of the Federal Food, Drug, and Cosmetic Act.

§ 251.2 Definitions.

The definitions of terms in section 804 of the Federal Food, Drug, and Cosmetic Act apply to the terms used in this part, if not otherwise defined in this section. The following definitions apply to this part:

Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug

product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

Adverse event means any untoward medical occurrence associated with the use of a drug product in humans, whether or not it is considered related to the drug product. An adverse event can occur in the course of the use of a drug product; from overdose of a drug product, whether accidental or intentional; from abuse of a drug product (e.g., physiological withdrawal); and includes any failure of expected pharmacological action.

Combination product has the meaning set forth in § 3.2(e) of this chapter.

Constituent part has the meaning set forth in § 4.2 of this chapter.

Disability means a substantial disruption of a person's ability to conduct normal life functions.

Eligible prescription drug means a drug subject to section 503(b) of the Federal Food, Drug, and Cosmetic Act that has been approved and has received a Notice of Compliance and a Drug Identification Number (DIN) from the Health Products and Food Branch of Health Canada (HPFB) and, but for the fact that it deviates from the required U.S. labeling, also meets the conditions in an FDA-approved new drug application (NDA) or abbreviated new drug application (ANDA) for a drug that is currently marketed in the United States, including those relating to the drug substance, drug product, production process, quality controls, equipment, and facilities.

Exclusion. The term *eligible prescription drug* does not include:

(1) A controlled substance (as defined in section 102 of the Controlled Substances Act (21 U.S.C. 802));

- (2) A biological product (as defined in section 351 of the Public Health Service Act (42 U.S.C. 262));
- (3) An infused drug (including a peritoneal dialysis solution);
- (4) An intravenously injected drug;
- (5) A drug that is inhaled during surgery;
- (6) An intrathecally or intraocularly injected drug;
- (7) A drug that is subject to a risk evaluation and mitigation strategy under section 505-1 of the Federal Food, Drug, and Cosmetic Act;
- (8) A drug that is not a “product” for purposes of section 582 as defined in section 581(13) of the Federal Food, Drug, and Cosmetic Act;

Entry means the information or data filed electronically to the Automated Commercial Environment (ACE) or any other U.S. Customs and Border Protection (CBP)-authorized electronic data interchange system to secure the release of imported merchandise from CBP, or the act of filing that information or data.

Foreign Seller means an establishment within Canada engaged in the distribution of an eligible prescription drug that is imported or offered for importation into the United States. A Foreign Seller must have an active drug establishment license as a drug wholesaler by Health Canada. A Foreign Seller must be registered with provincial pharmacy regulatory authorities to distribute HPFB-approved drugs. A Foreign Seller must not be licensed by a provincial pharmacy regulatory authority with an international pharmacy license that allows it to distribute drugs that are approved by countries other than Canada and that are not HPFB-approved for distribution in Canada. A Foreign Seller must also be registered with FDA under section 804 of

the Federal Food Drug and Cosmetic Act in accordance with the requirements described in this part.

Illegitimate foreign product means a drug purchased by a Foreign Seller from a manufacturer, and intended for sale to the Importer in the United States, where the Foreign Seller has credible evidence that the product:

- (1) Is counterfeit, diverted, or stolen;
- (2) Is intentionally adulterated such that the product would result in serious adverse health consequences or death to humans;
- (3) Is the subject of a fraudulent transaction; or
- (4) Appears otherwise unfit for distribution such that the product would be reasonably likely to result in serious adverse health consequences or death to humans.

Importer means a pharmacist or wholesaler. An Importer must be a State-licensed pharmacist, or a State or FDA-licensed wholesaler, who is the U.S. owner of an eligible prescription drug at the time of entry into the United States. An Importer's pharmacist or wholesaler license must be in effect (i.e., not expired) and the Importer must be in good standing with the licensor.

Individual case safety report (ICSR) means a description of an adverse event related to an individual patient or subject and/or a description of a medication error.

ICSR attachments means any document related to the adverse event or medication error described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

Life-threatening adverse event means any adverse event that places the patient, in the view of the initial reporter, at *immediate* risk of death from the adverse event as it occurred, i.e.,

it does not include an adverse event that, had it occurred in a more severe form, might have caused death.

Manufacturer means an applicant, as defined in § 314.3 of this chapter, or a person who owns or operates an establishment that manufactures an eligible prescription drug. *Manufacturer* also means a holder of a drug master file containing information necessary to authenticate an eligible prescription drug.

Medication error means any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare professional, patient, or consumer. The medication error may or may not result in an adverse event.

Minimum data set for an adverse event means the minimum four elements required for reporting an ICSR of an adverse event: An identifiable patient, an identifiable reporter, a suspect drug product, and an adverse event.

Minimum data set for a medication error means the minimum three elements required for reporting an ICSR of a medication error: An identifiable reporter, a suspect drug product, and a medication error.

Pre-Import Request means a request made to FDA by an Importer that must be granted by FDA before the Importer can start importation under a Section 804 Importation Program.

Qualifying laboratory means a laboratory in the United States that has been approved by FDA for the purposes of section 804 of the Federal Food, Drug, and Cosmetic Act.

Relabel has the meaning set forth in § 207.1 of this chapter.

Relabeler has the meaning set forth in § 207.1 of this chapter.

Repack or repackage has the meaning set forth in § 207.1 of this chapter.

Section 804 Importation Program (“SIP”) means a program under section 804 of the Federal Food, Drug, and Cosmetic Act that has been authorized by FDA for the importation of eligible prescription drugs from Canada.

Section 804 Importation Program Sponsor (“SIP Sponsor”): (Option 1): means a State, tribal, or territorial governmental entity that regulates wholesale drug distribution and/or the practice of pharmacy, and a co-sponsor or co-sponsors, if any, that submits a proposal to FDA that describes a program to facilitate the importation of prescription drugs from Canada under section 804 of the Federal Food, Drug, and Cosmetic Act. A co-sponsor must be a State, tribal, or territorial governmental entity, a pharmacist, or a wholesaler.

Section 804 Importation Program Sponsor (“SIP Sponsor”): (Option 2): means a State, tribal, or territorial governmental entity that regulates wholesale drug distribution and/or the practice of pharmacy, a wholesaler, or a pharmacist, and a co-sponsor or co-sponsors, if any, that submits a proposal to FDA that describes a program to facilitate the importation of prescription drugs from Canada under section 804 of the Federal Food, Drug, and Cosmetic Act. A co-sponsor must be a State, tribal, or territorial governmental entity, a wholesaler, or a pharmacist.

Section 804 Serial Identifier (“SSI”) means a unique alphanumeric serial number of up to 20 characters that is assigned and affixed by the Foreign Seller to each package and homogenous case of the product that it intends to sell to the Importer. For purposes of the SSI, “package” means the smallest individual saleable unit of product for distribution that is intended by the Foreign Seller for sale to the Importer located in the United States, and “individual saleable unit” means the smallest container of product sold by the Foreign Seller to the Importer.

Serious adverse event. (1) An adverse event is considered “serious” if it results in any of the following outcomes:

(i) Death;

(ii) A life-threatening adverse event where the patient was at immediate risk of death at the time of the event; it does not include an adverse event that might have caused death had it occurred in a more severe form;

(iii) Inpatient hospitalization or prolongation of existing hospitalization;

(iv) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; and/or

(v) A congenital anomaly/birth defect.

(2) Other events that may be considered serious adverse events: Important medical events that may not result in one of the listed outcomes in this definition may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient or study subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples include: Allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of product dependency or product abuse.

Statutory Testing means the testing of an eligible prescription drug for authenticity, degradation, and to ensure that the prescription drug is in compliance with established specifications and standards, as required by section 804(d)(1)(J) and (L) of the Federal Food, Drug, and Cosmetic Act.

Suspect foreign product means a drug purchased by the Foreign Seller from the manufacturer, and intended for sale to the Importer in the United States, that the Foreign Seller has reason to believe is:

(1) Potentially counterfeit, diverted, or stolen;

(2) Potentially intentionally adulterated such that the product would result in serious adverse health consequences or death to humans;

(3) Is potentially the subject of a fraudulent transaction; or

(4) Appears otherwise unfit for distribution such that the product would result in serious adverse health consequences or death to humans.

Transaction means the transfer of product between persons in which a change of ownership occurs.

Unexpected adverse event means an adverse event that is not included in the current U.S. labeling for the drug product. Events that may be symptomatically and pathophysiologically related to an adverse event included in the labeling but differ from the labeled event because of greater severity or specificity, would be considered unexpected. “Unexpected,” as used in this definition, also refers to adverse events that are mentioned in the product labeling as occurring with a class of products or anticipated from the pharmacological properties of the product but are not specifically mentioned as occurring with the particular product.

(1) *Example of greater severity.* Under this definition, hepatic necrosis would be unexpected if the labeling referred only to elevated hepatic enzymes or hepatitis.

(2) *Example of greater specificity.* Cerebral thromboembolism and cerebral hemorrhage would be unexpected if the labeling included only cerebrovascular accidents.

Unique facility identifier means the identifier required to be submitted by the registrant for drug establishment registration under section 510(b) of the Federal Food, Drug, and Cosmetic Act in accordance with § 207.25 of this chapter.

Wholesaler means a person licensed as a wholesaler or distributor of prescription drugs in the United States under section 503(e)(1) of the Federal Food, Drug, and Cosmetic Act. The term “wholesaler” does not include a person authorized to import drugs under section 801(d)(1).

Subpart B--Section 804 Importation Program Proposals and Pre-Import Requests

§ 251.3 SIP proposal submission requirements.

(a) A SIP Sponsor must only designate one Foreign Seller and one Importer per initial proposal. Additional Foreign Sellers and Importers may be added to an authorized SIP through a supplement under § 251.8.

(b) A SIP Sponsor that intends to implement a SIP under this part must submit a proposal to FDA in electronic form to FDA’s Electronic Submissions Gateway (ESG) or to an alternative transmission point identified by FDA. The proposal must include:

(1) A cover sheet containing the following:

(i) Name or names of SIP Sponsor and co-sponsors, if any; and

(ii) Name and contact information for a person authorized to serve as the point of contact with FDA during its review of the proposal;

(2) A table of contents;

(3) An introductory statement that includes an overview of the SIP Sponsor’s SIP Proposal; and

(4) The SIP Sponsor’s importation plan.

(c) The overview of the SIP Proposal must include:

(1) The name or names and address or addresses of the SIP Sponsor and co-sponsors, if any;

(2) The name and DIN of each eligible prescription drug that the SIP Sponsor seeks to include in the SIP;

(3) The name and address of the applicant that owns the approved NDA or ANDA for each eligible prescription drug's FDA-approved counterpart, and the approved NDA or ANDA number;

(4) The name and address of the manufacturer of the finished dosage form of the drug, if available;

(5) The name and address of the manufacturer of the active ingredient or ingredients of the drugs, if available;

(6) The name and address of the Foreign Seller;

(7) The name and address of the Importer;

(8) The name and address of the FDA-registered repackager or relabeler, if different from the Importer, that will relabel the eligible prescription drugs (including any limited repackaging in accordance with the requirements in this part), along with evidence of registration and of satisfactory resolution of any objectionable conditions or practices identified during its most recent FDA inspection, if applicable;

(9) A summary of how the SIP Sponsor will ensure:

(i) That the imported eligible prescription drugs meet the Statutory Testing requirements;

(ii) That the supply chain is secure;

(iii) That the labeling requirements of the Federal Food, Drug, and Cosmetic Act and this part are met;

(iv) That the post-importation pharmacovigilance and other requirements of the Federal Food, Drug, and Cosmetic Act and this part are met; and

(v) That the SIP Proposal would result in a significant reduction in the cost to the American consumer of the prescription drugs that the SIP Sponsor seeks to import.

(d) The SIP Sponsor's importation plan must:

(1) Identify the SIP Sponsor, including any co-sponsors, and identify the finished dosage form manufacturer of each prescription drug that the SIP Sponsor seeks to include in the SIP, the Foreign Seller, and the Importer, and explain the legal relationship of each of these entities to the SIP Sponsor, if any.

(2) Include an attestation containing a complete disclosure of any past criminal convictions or violations of the State, Federal, or Canadian laws regarding drugs or devices against the Foreign Seller or Importer or an attestation that the Foreign Seller or Importer has not been involved in, or convicted of, any such criminal or prohibited acts. Such attestation must include principals, any shareholder who owns 10 percent or more of outstanding stock in any non-publicly held corporation, directors, officers, and any facility manager or designated representative of such manager.

(3) Include a list of all disciplinary actions, to include the date of, and parties to, any action imposed against the Foreign Seller or the Importer by State, Federal, or Canadian regulatory bodies, including any such actions against the principals, owners, directors, officers, or any facility manager or designated representative of such manager for the previous 7 years prior to submission of the SIP Proposal.

(4) Include:

(i) the Health Canada inspectional history for the previous 5 years, or if the Foreign Seller has been licensed for less than 5 years, for the duration of its period of licensure; and

(ii) the State and Federal inspectional history for the Importer for the previous 5 years, or if the Foreign Seller has been licensed for less than 5 years, for the duration of its period of licensure.

(5) Include the proprietary and established names, the approved application numbers, and the DIN and National Drug Code (NDC), for each eligible prescription drug that the SIP Sponsor seeks to import from Canada and for its FDA-approved counterpart. It must also include as much of the information that is required by § 251.5 about the HPFB-approved product and its FDA-approved counterpart as is available, including the name and quantity of the active ingredient, the inactive ingredients, and the dosage form.

(6) Confirm that each HPFB-approved drug's FDA-approved counterpart drug is currently marketed in the United States.

(7) Describe, to the extent possible, the testing that will be done to establish that the HPFB-approved drug meets the conditions in the NDA or ANDA for the HPFB-approved drug's FDA-approved counterpart. It must also identify the qualifying laboratory that will conduct the testing, and it must establish that the laboratory is qualified in accordance with § 251.15 to conduct the tests.

(8) Include a copy of the FDA-approved labeling for the FDA-approved version of the eligible prescription drug, a copy of the proposed labeling that will be used for the eligible prescription drug, and a side-by-side comparison of the FDA-approved labeling and the proposed labeling including, if applicable, any patient labeling, with all differences annotated and explained. The SIP Proposal must also include a copy of the HPFB-approved labeling.

(9) Explain how the SIP Sponsor expects that the SIP will result in a significant reduction in the cost to the American consumer of the prescription drugs that the SIP Sponsor seeks to

import. The explanation must include any assumptions and uncertainty, and it must be sufficiently detailed to allow for a meaningful evaluation.

(10) Explain how the SIP Sponsor will ensure that all of the participants in the SIP comply with the requirements of section 804 of the Federal Food, Drug, and Cosmetic Act and this part.

(11) Describe the procedures the SIP Sponsor will use to ensure that the requirements of this part are met, including the steps that will be taken to ensure that the:

(i) Storage, handling, and distribution practices of supply chain participants, including transportation providers, meet the minimum requirements of part 205 of this chapter and do not affect the quality or impinge on the security of the eligible prescription drugs;

(ii) Supply chain is secure;

(iii) Importer screens the eligible prescription drugs it imports for evidence that they are adulterated, counterfeit, damaged, tampered with, or expired; and

(iv) Importer fulfills its responsibilities to submit adverse event, medication error, field alert, and other reports.

(12) Explain how the SIP Sponsor will educate pharmacists, healthcare providers, and patients about the drugs imported under its SIP.

(13) Include the SIP's recall plan, including an explanation of how the SIP Sponsor will obtain recall or market withdrawal information and how it will ensure that recall or market withdrawal information is shared among the SIP Sponsor, the Foreign Seller, the Importer, and FDA and provided to the manufacturer; and

(14) Explain how the SIP Sponsor will ensure that any information that the manufacturer provides to the Importer to allow the Importer to conduct the Statutory Testing, or information

otherwise obtained by the Importer for such purposes, would be kept in strict confidence and used only for purposes of testing or otherwise complying with the Federal Food, Drug, and Cosmetic Act, as required by section 804(e)(2)(B).

§ 251.4 Review and authorization of importation program proposals.

Based on a review of a SIP Proposal submitted under this part, FDA may authorize, modify, or extend the authorization period of a SIP that meets the requirements of this part. FDA may deny a request for authorization, modification, or extension of a SIP in its discretion, including if a proposed SIP does not meet the standard for authorizing a SIP under this part. Where a SIP Proposal meets the requirements of this part, FDA may nonetheless decide, in its discretion, not to authorize the SIP Proposal.

(a) Among other reasons, FDA may decide not to authorize a SIP Proposal because of potential safety concerns with the SIP, because of the degree of uncertainty that the SIP Proposal would adequately ensure the protection of public health, because, based on the recommendation of another Health and Human Services (HHS) component as directed by the Secretary, the relative likelihood that the SIP Proposal would not result in significant cost savings, or in order to limit the number of authorized SIP programs so FDA can effectively and efficiently carry out its responsibilities under section 804 of the Federal Food, Drug, and Cosmetic Act in light of the amount of resources allocated to carrying out such responsibilities.

(b) FDA will notify a SIP Sponsor in writing, including through electronic means, when FDA receives the SIP Sponsor's SIP Proposal.

(c) FDA will make a reasonable effort to promptly communicate to a SIP Sponsor about any information required by § 251.3 that was not submitted in a SIP Proposal.

(1) FDA may notify a SIP Sponsor if FDA believes additional information would help FDA's review of a SIP Proposal.

(2) FDA will notify a SIP Sponsor in writing, including through electronic means, whether FDA has decided to authorize or not to authorize the SIP Sponsor's SIP Proposal.

§ 251.5 Pre-Import Request.

(a) A prescription drug may not be imported or offered for import under this part unless the Importer has filed a Pre-Import Request for that drug, which has been granted by FDA.

(b) The Importer must submit a complete Pre-Import Request at least 30 days prior to scheduled date of arrival or entry for consumption, whichever occurs first, of an eligible prescription drug covered under an authorized SIP.

(c) A complete Pre-Import Request must include, at a minimum:

(1) Identification of the Importer including Importer name, business type (wholesale distributor or pharmacist), U.S. license number(s) and State(s) of license, business address, unique facility identifier if required to register with FDA as an establishment under section 510 of the Federal Food, Drug, and Cosmetic Act or FDA establishment identification number if not required to register under section 510 of the Federal Food, Drug, and Cosmetic Act, and name of a contact person with their email and phone number.

(2) Identification of the FDA-authorized SIP including the name of the SIP; the name or names of the SIP Sponsor and co-sponsors, if any; business address; and the name, email address, and phone number of a contact person.

(3) Identification of the Foreign Seller, including the name of the Foreign Seller, business address, unique facility identifier, any license numbers issued by Health Canada or a provincial pharmacy regulatory body, and the name, email address, and phone number of a contact person.

(4) Identification and description of the drug(s) covered by the Pre-Import Request, including the following information:

(i) Established and trade name of the HPFB-approved drug(s), as applicable, DIN, and complete product description including strength, description of dosage form, and route of administration.

(ii) Active pharmaceutical ingredient (API) information, including:

(A) Name of API;

(B) Manufacturer of API and its unique facility identifier; and

(C) Amount of API and unit measure in each eligible prescription drug;

(iii) Established name and trade name, as applicable, of FDA-approved counterpart drug(s) and NDA or ANDA number.

(iv) Manufacturer of the eligible prescription drug with the business address and unique facility identifier.

(v) Copies of the invoice and any other documents related to the manufacturer's sale of the drugs to the Foreign Seller provided by the manufacturer to the Importer, and copies of the same documents provided by the Foreign Seller to the Importer.

(vi) Quantity, listed separately by dosage form, strength, batch and lot or control number assigned by the manufacturer to each eligible prescription drug intended to be imported under this Pre-Import Request compared to the quantity of each batch and lot or control number originally received by the Foreign Seller from the manufacturer, and the date of such receipt.

(vii) Expiration date of each HPFB-approved drug, listed by lot or control number.

(viii) Expiration date to be assigned to the eligible prescription drug when relabeled by the Importer with a complete description of how that expiration date was calculated to comply with the FDA-approved NDA or ANDA.

(ix) NDC proposed for assignment by the Importer.

(x) FDA product code for the eligible prescription drug(s) to be imported.

(xi) A Statutory Testing plan that includes:

(A) A description of how the samples will be selected from a shipment for the Statutory Testing;

(B) The name and location of the qualifying laboratory in the United States that will conduct the Statutory Testing; and

(C) A description of the testing method(s) that will be used to conduct the Statutory Testing, if the Importer will be conducting the Statutory Testing, or the description of the testing methods must be submitted by the manufacturer to FDA directly under § 251.17 if the manufacturer will be conducting the Statutory Testing.

(xii) Attestation from the manufacturer that must establish that the drug proposed for import, but for the fact that it bears the HPFB-approved labeling, meets the conditions in the FDA-approved NDA or ANDA, including any process-related or other requirements for which compliance cannot be established through laboratory testing. Accordingly, the attestation must include:

(A) Confirmation that the HPFB-approved drug has the active ingredient(s), active ingredient source(s) (including manufacturing facility or facilities), inactive ingredient(s), dosage form, strength(s), and route(s) of administration, described in the FDA-approved drug's NDA or ANDA.

(B) Confirmation that the HPFB-approved drug conforms to the specifications in the FDA-approved drug's NDA or ANDA regarding the quality of the drug substance(s), drug product, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of the drug.

(C) Confirmation that the HPFB-approved drug was manufactured in accordance with the specifications described in the FDA-approved drug's NDA or ANDA, including with regard to the facilities and manufacturing lines that are used, and in compliance with current good manufacturing practice requirements set forth in section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and parts 4 (if a combination product), 210, and 211 of this chapter.

(D) Original date of manufacture or the date used to calculate the labeled expiration date based on the HPFB-approved or scientifically validated expiration period, the expiration period set forth in the FDA-approved drug's NDA or ANDA, and any other information needed to label the drug with an expiration date that meets the specifications of the FDA-approved drug's NDA or ANDA.

(E) Information needed to confirm that the labeling of the prescription drug complies with labeling requirements of the Federal Food, Drug, and Cosmetic Act.

(xiii) Information related to the Importation, including:

(A) Location of the eligible prescription drugs in Canada and anticipated date of shipment (date eligible prescription drug(s) will leave their location in Canada);

(B) Name, address, email, and telephone number of the Foreign Shipper;

(C) Anticipated date of export from Canada and Canadian port of exportation;

(D) Anticipated date and approximate time of arrival at a port authorized by FDA to import eligible prescription drugs under section 804 of the Federal Food, Drug, and Cosmetic Act;

(E) The name, address, unique facility identifier or FDA establishment identification number, and telephone number of the warehouse, location within a specific foreign trade zone, or other secure distribution facility controlled by or under contract with the Importer where the eligible prescription drug(s) will be stored pending testing, relabeling, and FDA determination of admissibility;

(F) Information regarding the facility where the relabeling and any limited repackaging activities will occur for all eligible prescription drugs covered by this Pre-Import Request, including:

(1) The facility's unique facility identifier;

(2) The facility's name, address, and FDA establishment identifier number;

(3) The anticipated date the relabeling and any limited repackaging will be completed;

and

(4) Information about where the relabeled drug will be stored pending distribution, including the FDA establishment identification number of the storage facility, if available.

(d) If the manufacturer conducts the Statutory Testing, the manufacturer must provide the attestation to FDA. If the Importer conducts the Statutory Testing, the manufacturer must provide the attestation to the Importer.

(e)(1) The Importer must provide the executed batch record, including the executed certificate of analysis for at least one recently manufactured, commercial-scale batch of the HPFB-approved drug; and at least one recently manufactured, commercial-scale batch of the

FDA-approved drug that was produced for and released for distribution to the U.S. market under an NDA or ANDA.

(2) The manufacturer must provide these analyses for each manufacturing line that the manufacturer used to produce either or both of the drugs.

§ 251.6 Limitations on authorized importation programs.

(a) Unless an extension is granted under this section, authorization for a SIP automatically terminates after 2 years, or a shorter period of time if a shorter period of time is specified in the authorization for the SIP.

(b) The 2-year authorization period for a SIP begins when the Importer files an electronic import entry for consumption for its first shipment of drugs under the SIP.

(c) Notwithstanding paragraph (a) of this section, authorization for a SIP terminates if the Importer does not file an electronic import entry for consumption for a shipment of eligible prescription drugs under the SIP within 1 year of the date that the SIP was authorized.

(d) FDA will terminate authorization of a SIP upon request from the SIP Sponsor that includes a notice of the SIP Sponsor's intent to discontinue its activities.

§ 251.7 Suspension and revocation of authorized importation programs.

(a) FDA may suspend a SIP under the circumstances set forth in § 251.18, or under other circumstances in FDA's discretion. Importation of drugs under a SIP that has been suspended is prohibited.

(b) SIP Sponsors and other SIP participants must agree to submit to audits of their books and records and inspections of their facilities as a condition of participation in a SIP. If a SIP Sponsor, manufacturer, Foreign Seller, Importer, qualifying laboratory, or other participant in the supply chain delays, denies, or limits an inspection, or refuses to permit entry or inspection of

their facility or their records, any drug that has been held by such entity will be deemed to be adulterated and the SIP may be suspended, in whole or in part, immediately.

(c) FDA may revoke authorization of a SIP, in whole or in part, including with respect to one or more drugs in the SIP, at any time for any reason if FDA determines, in its discretion, or on the recommendation of another HHS component as directed by the Secretary, that:

(1) The SIP Proposal contained an untrue statement of material fact;

(2) The SIP Proposal omitted material information;

(3) The SIP no longer meets the requirements of section 804 of the Federal Food, Drug, and Cosmetic Act, this part, or the SIP, including, among other things, if the manufacturer, the Foreign Seller, the Importer, or any other SIP entity is found to be not compliant with section 501(a)(2)(A) or (B) of the FD&C Act;

(4) Continued implementation of the SIP is likely to pose additional risk to the public's health and safety;

(5) Confidential manufacturer information was disclosed in violation of § 251.16;

(6) Continued implementation of the SIP will not result in a significant reduction in the cost of the drugs covered by the SIP to the American consumer;

(7) Continued monitoring of the SIP imposes too much of a drain on FDA or HHS resources or is inconsistent with FDA or HHS prioritization of resources; or

(8) Continued implementation of the SIP is otherwise inappropriate.

§ 251.8 Modification or extension of authorized importation programs.

(a) A supplement to modify or extend an authorized SIP must be submitted via the ESG for FDA's consideration.

(b) A SIP Sponsor can propose to add additional Foreign Sellers or additional Importers to an authorized SIP once it has consistently imported eligible prescription drugs in accordance with section 804 of the Federal Food, Drug, and Cosmetic Act and this part.

(c) If FDA authorizes changes to the SIP, the Importer must submit a new Pre-Import Request in accordance with § 251.5.

(d) A SIP Sponsor must not make any changes or permit any changes to be made to a SIP without first securing FDA's authorization. If FDA authorizes changes to a SIP under this section, such authorization does not change the authorization of the original SIP.

(e) A SIP Sponsor may request that FDA extend the authorization period of an authorized SIP. Such a request must be submitted via the ESG for FDA's consideration at least 3 months before the SIP's authorization period will expire. To be eligible for an extension of the authorized SIP, a SIP must be up to date on all of the information and records-related requirements of section 804 of the Federal Food, Drug, and Cosmetic Act and this part. FDA may, in its sole discretion, extend the authorization period for up to 2 years at a time.

Subpart C: Certain Requirements for Section 804 Importation Programs

§ 251.9 Registration of Foreign Sellers.

(a) Foreign Sellers must be registered with FDA before FDA will authorize a SIP Proposal.

(b) To register, a Foreign Seller must provide the following information:

(1) Name of the owner or operator; if a partnership, the name of each partner; if a corporation, the name of each corporate officer and director, and the place of incorporation;

(2) All names of the Foreign Seller, including names under which the Foreign Seller conducts business or names by which the Foreign Seller is known;

- (3) Physical address, telephone number(s), and email address of the Foreign Seller;
- (4) Registration number, if previously assigned by FDA;
- (5) A copy of the Foreign Seller's Health-Canada Drug Establishment License;
- (6) All types of operations performed by the Foreign Seller;
- (7) Name, mailing address, telephone number, and email address of the official contact

for the establishment; and

(8) Name, mailing address, telephone number, and email address of:

- (i) The U.S. agent;
- (ii) The Importer to which the Foreign Seller plans to sell eligible prescription drugs; and
- (iii) Each SIP Sponsor with which the Foreign Seller works.

§ 251.10 Reviewing and updating registration information for Foreign Sellers.

(a) *Expedited updates.* A Foreign Seller must update its registration information no later than 30 calendar days after:

- (1) Closing or being sold;
- (2) Changing their name or physical address; or
- (3) Changing the name, mailing address, telephone number, or email address of the

official contact or the U.S. agent. A Foreign Seller, official contact, or U.S. agent may notify FDA about a change of information for the designated official contact or U.S. agent, but only a Foreign Seller is permitted to designate a new official contact or U.S. agent.

(b) *Annual review and update of registration information.* A Foreign Seller must review and update all registration information required under § 251.9.

(1) The first review and update must occur during the period beginning on October 1 and ending December 31 of the year of initial registration, if the initial registration occurs prior to

October 1. Subsequent reviews and updates must occur annually, during the period beginning on October 1 and ending December 31 of each calendar year.

(2) The updates must reflect new changes not previously required to be reported along with a summary of the registration updates that were provided to FDA as required during the calendar year.

(3) If no changes have occurred since the last registration, a Foreign Seller must certify that no changes have occurred.

§ 251.11 Official contact and U.S. agent for Foreign Sellers.

(a) *Official contact.* A Foreign Seller subject to the registration requirements of this part must designate an official contact. The official contact is responsible for:

(1) Ensuring the accuracy of registration information as required by § 251.9; and

(2) Reviewing, disseminating, routing, and responding to all communications from FDA, including emergency communications.

(b) *U.S. agent.* (1) A Foreign Seller must designate a single U.S. agent. The U.S. agent must reside or maintain a place of business in the United States and may not be a mailbox, answering machine or service, or other place where a person acting as the U.S. agent is not physically present. The U.S. agent is responsible for:

(i) Reviewing, disseminating, routing, and responding to all communications from FDA, including emergency communications;

(ii) Responding to questions concerning those drugs that are imported or offered for import to the United States; and

(iii) Assisting FDA in scheduling inspections.

(2) FDA may provide certain information and/or documents to the U.S. agent. The provision of information and/or documents by FDA to the U.S. agent is equivalent to providing the same information and/or documents to the Foreign Seller.

§ 251.12 Importer responsibilities.

(a) The Importer is responsible for:

(1) In accordance with the procedures set forth in § 207.33 of this chapter, proposing an NDC for assignment for each eligible prescription drug imported pursuant to this part;

(2) Examining the Canadian labeling of a sample of each shipment of eligible prescription drugs to verify that the labeling is consistent with that of an HPFB-approved drug, and attesting that such examination has been conducted through reports to FDA required under this part;

(3) Screening eligible prescription drugs for evidence that they are adulterated, counterfeit, damaged, tampered with, or expired;

(4) Ensuring the eligible prescription drug is relabeled with the required U.S. labeling, including the container and carton labels; prescribing information; and patient labeling, such as medication guides, instruction for use documents, and patient package inserts, in accordance with §§ 251.13 and 251.14(d);

(5) Arranging for an entry to be submitted in accordance with § 251.17;

(6) Collecting and submitting the information and documentation to FDA about the imported drug(s) pursuant to section 804(d) of the Federal Food, Drug, and Cosmetic Act, in addition to information about the Foreign Seller, as set forth in § 251.19; and

(7) Submitting the adverse event, medication error, field alert, and other reports, and complying with drug recalls, in accordance with § 251.18.

(b) If the Importer is also relabeling the eligible prescription drug, the Importer must also:

(1) Register with FDA as a repackager or relabeler under section 510(b) of the Federal Food, Drug, and Cosmetic Act, in accordance with § 207.25 of this chapter;

(2) Obtain a labeler code from FDA and propose an NDC for each eligible prescription drug pursuant to § 207.33 of this chapter; and

(3) List each eligible prescription drug pursuant to § 207.53 of this chapter.

(c) If the Importer is not itself relabeling the eligible prescription drug, the Importer must:

(1) Obtain its own labeler code from FDA under § 207.33(c) of this chapter;

(2) Ensure that the eligible prescription drug incorporates the NDC the Importer proposed for assignment, which must include the Importer's labeler code; and

(3) Ensure that the entity relabeling an eligible prescription drug on its behalf proposes an NDC pursuant to § 207.33 of this chapter and lists each eligible prescription drug pursuant to § 207.53 of this chapter.

§ 251.13 Labeling of eligible prescription drugs.

(a) Upon the request of a SIP Sponsor or Importer, the manufacturer of a prescription drug must provide an Importer written authorization for the Importer to use, at no cost, the FDA-approved labeling for the prescription drug. If the manufacturer fails to do so within a timely fashion, FDA may deem this authorization to have been given.

(b) In addition to the exemption provided in subpart D of part 201 of this chapter, an eligible prescription drug imported for purposes of this part is exempt from section 502(f)(1) of the Federal Food, Drug, and Cosmetic Act if all the following conditions are met:

(1) The Importer or the manufacturer certifies that the drug meets all labeling requirements under the Federal Food, Drug, and Cosmetic Act, including the requirements of this part. The Importer of an eligible prescription drug must either:

(i) Propose an NDC for the drug following the procedures in § 207.33 of this chapter and list the drug following the procedures in § 207.53 of this chapter, or

(ii) If the Importer is a private label distributor, take responsibility to ensure that the entity performing relabeling on its behalf proposes an NDC and lists each eligible prescription drug in accordance with the applicable requirements of part 207 of this chapter.

(2) The drug must be:

(i) In the possession of a person (or his agents or employees), including Foreign Sellers and Importers, regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale distribution of prescription drugs;

(ii) In the possession of a retail, hospital, or clinic pharmacy, or a public health agency, regularly and lawfully engaged in dispensing prescription drugs; or

(iii) In the possession of a practitioner licensed by law to administer or prescribe such drugs.

(3) The drug is to be dispensed in accordance with section 503(b) of the Federal Food, Drug, and Cosmetic Act.

(4) The label of the drug must be the same as the label authorized by the approved NDA or ANDA of the FDA-approved drug, except that the label must bear conspicuously:

(i) The Importer's NDC for the eligible prescription drug, and such NDC must replace any other NDC otherwise appearing on the label of the FDA-approved drug; and

(ii) The name and place of business of the manufacturer and the Importer.

(5) The container label must include at a minimum the product's proprietary and established name (if any); product strength; lot number; and the name of the manufacturer and the Importer.

(6) Labeling on or within the package from which the eligible prescription drug is to be dispensed is the same as the labeling authorized by the NDA or the ANDA of the FDA-approved drug, except that:

(i) The labeling must bear the statement: "This drug was imported from Canada under the [Name of State or Other Governmental Entity and of Its Co-Sponsors, If Any] Section 804 Importation Program to reduce its cost to the American consumer." If the SIP maintains a website, the statement could also include the website address. This statement must be included after the PATIENT COUNSELING INFORMATION section for products subject to §§ 201.56(d) and 201.57 of this chapter, or after the HOW SUPPLIED section (or after the last section of labeling) for products subject to §§ 201.56(e) and 201.80 of this chapter. The statement also must be included on the immediate container and outside package;

(ii) For products subject to §§ 201.56(d) and 201.57(c)(17)(iii) of this chapter, the NDC(s) assigned to the eligible prescription drug in accordance with the procedures in § 207.33 of this chapter must be included in the HOW SUPPLIED/STORAGE AND HANDLING section in place of the NDC(s) assigned to the FDA-approved U.S. versions of the drug; and

(iii) For products subject to §§ 201.56(e) and 201.80(k)(3) of this chapter, the NDC(s) assigned to the eligible prescription drug in accordance with the procedures in § 207.33 of this chapter must be included in the HOW SUPPLIED section in place of the NDC(s) assigned to the FDA-approved U.S. versions of the drug.

(c) The Importer is responsible for relabeling the drug, or arranging for it to be relabeled, to meet the requirements of this part. The relabeling and associated limited repackaging activities must meet applicable requirements, including applicable current good manufacturing practice requirements under parts 210 and 211 of this chapter. Except for repackaging that is necessary to perform the relabeling described in this part, further repackaging of drugs imported pursuant to a SIP is prohibited.

§ 251.14 Supply chain security requirements for eligible prescription drugs.

(a) *SIP Sponsors.* A sponsor of an authorized SIP must ensure that:

(1) Each drug imported under the SIP is HPFB-approved and labeled for sale in Canada from the point of manufacture until it reaches the Foreign Seller;

(2) For each drug that is imported under the SIP and that is manufactured outside Canada, the drug was authorized for import into Canada by the manufacturer and labeled by the manufacturer for the Canadian market before importation under the SIP (i.e. the drug was not transshipped through Canada for sale in another country);

(3) For each drug imported under the SIP, the drug was sold by the manufacturer directly to a Foreign Seller;

(4) For each drug imported under the SIP, the Foreign Seller ships the drug directly to the Importer in the United States; and

(5) The Importer(s) and Foreign Seller(s) identified in the SIP meet the applicable requirements of this part and in section 582(c) and (d) of the Federal Food, Drug, and Cosmetic Act.

(b) *Manufacturer.* The manufacturer must provide to the Importer a copy of any transaction documents that were provided from the manufacturer to the Foreign Seller.

(c) *Foreign Seller.*

(1) A Foreign Seller must have systems in place to:

(i) Determine whether a drug in its possession or control that it intends to sell to the Importer under a SIP is a suspect foreign product. Upon making a determination that a drug in its possession or control is a suspect foreign product, or upon receiving a request for verification from FDA that the Foreign Seller has determined that a product within its possession or control is a suspect foreign product, a Foreign Seller must:

(A) Quarantine such product within its possession or control until such product is cleared or dispositioned;

(B) Promptly conduct an investigation, in coordination with the Importer and the manufacturer, as applicable, to determine whether the product is an illegitimate foreign product, and verify the product at the package level, including the SSI; and

(C) If the Foreign Seller makes the determination that a suspect foreign product is not an illegitimate foreign product, promptly notify FDA of such determination (such product may be further distributed).

(ii) Determine whether a drug in its possession or control that it intends to sell to the Importer under a SIP is an illegitimate foreign product. Upon making a determination that a drug in its possession or control is an illegitimate foreign product, the Foreign Seller must:

(A) Quarantine such product within the possession or control of the Foreign Seller from product intended for distribution until such product is dispositioned;

(B) Disposition the illegitimate foreign product within the possession or control of the Foreign Seller;

(C) Take reasonable and appropriate steps to assist a manufacturer or Importer to disposition an illegitimate product not in the possession or control of the Foreign Seller; and

(D) Retain a sample of the product for further physical examination or laboratory analysis of the product by the manufacturer or the Secretary (or other appropriate Federal or State official) upon request by the Secretary (or other appropriate Federal or State official), as necessary and appropriate.

(2)(i) Upon determining that a product in the possession or control of the Foreign Seller is an illegitimate foreign product, the Foreign Seller must notify FDA and the Importer that the Foreign Seller received such illegitimate product not later than 24 hours after making such determination.

(ii) Upon the receipt of a notification from FDA, the Importer, or other authorized repackager, wholesale distributor, or dispenser that a determination has been made that a product that had been sold by the Foreign Seller is an illegitimate foreign product, a Foreign Seller must identify all illegitimate foreign product subject to such notification that is in the possession or control of the Foreign Seller, including any product that is subsequently received, and perform the activities to investigate the product described in paragraph (c)(1) of this section.

(iii) Upon making a determination, in consultation with FDA, that a notification is no longer necessary, a Foreign Seller must promptly notify the Importer and person who sent the notification that the notification is terminated.

(iv) A Foreign Seller must keep records of the disposition of an illegitimate foreign product for not less than 6 years after the conclusion of the disposition.

(3) Upon request by FDA, or other appropriate Federal or State official, in the event of a recall or for purposes of investigating a suspect foreign product or an illegitimate foreign

product, a Foreign Seller must promptly provide the official with information about its transactions with the manufacturer and the Importer.

(4) A Foreign Seller, upon receiving a shipment of eligible prescription drugs from the manufacturer, must:

(i) Separate the portion of drugs intended for sale to the Importer located in the United States, and store such portion separately from that portion of product intended for sale in the Canadian market;

(ii) Assign a SSI to each package and homogenous case intended for sale to the Importer in the United States, unless each such package and homogenous case contains a manufacturer-affixed or imprinted product identifier, as such term is defined in section 581(14) of the Federal Food, Drug, and Cosmetic Act, at the time of receipt by the Foreign Seller; and

(iii) Affix or imprint the SSI on each package and homogenous case intended for sale to the Importer in the United States. Such SSI must be located on blank space on the package or homogenous case and must not obscure any labeling for the Canadian market, including the DIN.

(5) Upon receiving a request for verification from the Importer or other authorized repackager, wholesale distributor, or dispenser that is in possession or control of a product such person believes to be distributed by such Foreign Seller, a Foreign Seller must, not later than 24 hours after receiving the request for verification or in other such reasonable time as determined by the Secretary, based on the circumstances of the request, notify the person making the request whether the product identifier, including the standardized numerical identifier, that is the subject of the request corresponds to the SSI affixed or imprinted by the Foreign Seller. If a Foreign Seller responding to a request for verification identifies a product identifier that does not correspond to that SSI affixed or imprinted by the Foreign Seller, the Foreign Seller must treat

such product as suspect foreign product and conduct an investigation as described in paragraph (c)(1) of this section. If the Foreign Seller has reason to believe the product is an illegitimate foreign product, the Foreign Seller must advise the person making the request of such belief at the time such Foreign Seller responds to the request for verification.

(6) For each transaction between the Foreign Seller and the Importer for an eligible prescription drug, the Foreign Seller must provide:

- (i) A statement that the Foreign Seller received the product from an FDA-registered manufacturer;
- (ii) The proprietary or established name of the product;
- (iii) The strength and dosage form of the product;
- (iv) The container size;
- (v) The number of containers;
- (vi) The lot number of the product;
- (vii) The date of the transaction;
- (viii) The date of the shipment, if more than 24 hours after the date of the transaction;
- (ix) The business name and address of the person associated with the Foreign Seller from whom ownership is being transferred;
- (x) The business name and address of the person associated with the Importer to whom ownership is being transferred;
- (xi) The SSI for each package and homogenous case of product; and
- (xii) The Canadian DIN for each product transferred.

(7) Upon a request by FDA, or other appropriate Federal or State official, in the event of a recall or for purposes of investigating a suspect foreign product or an illegitimate foreign

product, the Foreign Seller must promptly provide the official with information about its transactions with the manufacturer and the Importer.

(d) Importers. (1) An Importer of an eligible prescription drug must purchase the drug directly from a Foreign Seller in Canada.

(2) Upon receipt of a product from the Foreign Seller, an Importer must facilitate the affixation or imprinting of a product identifier, as defined in section 581(14) of the Federal Food, Drug, and Cosmetic Act. The Importer must ensure that such affixation or imprinting occurs at the same time the product is relabeled with the required U.S.-approved labeling for the drug product and, except for repackaging necessary to perform the relabeling described in this part, cannot otherwise relabel or repackage the product. The Importer may contract with an entity registered with FDA under part 207 of this chapter to accomplish such relabeling, provided that the entity does not otherwise relabel or repackage the product, except for repackaging that is necessary to perform the relabeling described in this part.

(3) The repackager or relabeler that affixes or imprints the product identifier to each package and homogenous case of an eligible prescription drug in accordance with section 582 of the Federal Food, Drug, and Cosmetic Act--

(i) May affix or imprint a product identifier only on a package of an eligible prescription drug that has a serial number that was assigned and affixed by the Foreign Seller;

(ii) Must maintain the product identifier information for such drug for not less than 6 years; and

(iii) Must maintain records for not less than 6 years that associate the product identifier the repackager affixes or imprints with the serial number assigned by the Foreign Seller and the Canadian DIN.

(4) An Importer must retain records, for no less than 6 years, that allow the Importer to associate the product identifier affixed or imprinted on each package or homogenous case of product it received from the Foreign Seller, with the SSI that had been assigned by the Foreign Seller, and the Canadian DIN that was on the package when the Foreign Seller received the product from the original manufacturer. An Importer must also have processes in place to, upon receipt of a drug and records from a Foreign Seller, compare such information with information the Importer received from the manufacturer, including relevant documentation about the transaction that the manufacturer provided to the Foreign Seller upon its transfer of ownership of the product for the Canadian market.

(5) An Importer must comply with all applicable requirements of section 582 of the Federal Food, Drug, and Cosmetic Act, including requirements that apply to subsequent transactions with trading partners, unless a waiver, exception, or exemption applies.

(6) For transactions of eligible prescription drugs between Importers and Foreign Sellers, an Importer is exempt from the following supply chain security requirements that are otherwise applicable:

(i) An Importer is exempt from the prohibition on receiving a product for which the previous owner did not provide the transaction history, transaction information, and transaction statement, under section 582(c)(1)(A) or (d)(1)(A) of the Federal Food, Drug, and Cosmetic Act as applicable; provided that the Importer receives from the Foreign Seller the information required under paragraph (c) of this section.

(ii) An Importer is exempt from the prohibition on receiving a product that is not encoded with a product identifier, under section 582(c)(2) or (d)(2) of the Federal Food, Drug, and Cosmetic Act as applicable, provided that the product the Importer received from the Foreign Seller has an SSI.

(iii) An Importer is exempt from the prohibition on conducting a transaction with an entity that is not an “authorized trading partner,” under section 582(c)(3) or (d)(3) of the Federal Food, Drug, and Cosmetic Act as applicable.

(iv) An Importer is exempt from the requirement to verify that a product in the Importer’s possession or control contains a “standardized numerical identifier” at the package level, under section 582(c)(4)(A)(i)(II) or (d)(4)(A)(ii)(II) of the Federal Food, Drug, and Cosmetic Act as applicable, provided that the Importer verifies that each package and homogenous case of the product includes the SSI affixed or imprinted by the Foreign Seller.

§ 251.15 Qualifying laboratory requirements.

(a) To be considered a qualifying laboratory for purposes of section 804 of the Federal Food, Drug, and Cosmetic Act and this part, a laboratory must have ISO 17025 accreditation.

(b) To be considered a qualifying laboratory for purposes of section 804 of the Federal Food, Drug, and Cosmetic Act and this part, a laboratory must have an FDA inspection history and it must have satisfactorily addressed any objectionable conditions or practices identified during its most recent FDA inspection, if applicable.

(c) To be considered a qualifying laboratory for purposes of section 804 of the Federal Food, Drug, and Cosmetic Act and this part, a laboratory must comply with the applicable elements of current good manufacturing practice requirements, including but not limited to

provisions regarding laboratory controls in § 211.160 of this chapter and laboratory records in § 211.194 of this chapter.

§ 251.16 Laboratory testing requirements.

(a) The manufacturer or the Importer must arrange for eligible prescription drugs to be tested by a qualifying laboratory.

(b) If the tests are conducted by the Importer, the manufacturer of the prescription drug must supply to the Importer all information needed to authenticate the prescription drug being tested, including any necessary testing methodologies and protocols that the manufacturer has developed. The manufacturer must also provide the Importer with formulation information about the HPFB-approved drug and the FDA-approved drug to facilitate authentication.

(c) Testing done on a statistically valid sample of the batch or shipment, as applicable, must be sufficiently thorough to establish, in conjunction with data and information from the manufacturer, that the batch or shipment is eligible for importation under a SIP. The size of the sample must be large enough to enable a statistically valid statement to be made regarding the authenticity and stability of the quantity of the batch in the shipment or the entire shipment, as applicable.

(d) The statistically valid sample of the HPFB-approved drug must be subjected to testing to confirm that the HPFB-approved drug meets the FDA-approved drug's specifications, including the analytical procedures and methods and the acceptance criteria. In addition, to testing for degradation, a stability-indicating assay provided by the manufacturer must be conducted on the sample of the drug that is proposed for import.

(e) If the manufacturer performs the testing required under section 804(e)(1) of the Federal Food, Drug, and Cosmetic Act at a qualifying laboratory, the testing results, a complete

set of laboratory records, a detailed description of the selection method for the samples, the testing methods used, complete data derived from all tests necessary to ensure that the eligible prescription drug meets the specifications of the FDA-approved drug that are established in the NDA or ANDA, a Certificate of Analysis, and any other documentation demonstrating that the testing meets the requirements under section 804(e)(1) of the Federal Food, Drug, and Cosmetic Act must be submitted in electronic form directly to FDA via the ESG or to an alternative transmission point identified by FDA.

(f) Regardless of whether testing under this section is performed by the manufacturer or Importer, the sample of a batch or shipment of drugs must be randomly selected for testing or, in the alternative, the sample must be selected to be representative of the quantity of the batch in a shipment or of a shipment, as applicable.

(g) Information supplied under this part must be kept in strict confidence by the recipient and only for the purpose of testing or otherwise complying with this part.

(h) To ensure that trade secret and commercial or financial information is protected:

(1) The information that the manufacturer provides must not be disseminated except to the qualifying laboratory and to FDA; and

(2) The SIP Sponsor must explain how it will ensure that the information is not disseminated beyond the qualifying laboratory.

(i) FDA may transmit information that the manufacturer is required to provide to an Importer under this section on the manufacturer's behalf if the manufacturer has not transmitted such information to the Importer in a timely fashion and if such information is available to FDA in the NDA or ANDA.

§ 251.17 Importation requirements.

(a) Importers must ensure that each shipment of eligible prescription drugs imported or offered for import pursuant to this part is accompanied by an import entry for consumption filed electronically as a formal entry in ACE, or another CBP-authorized electronic data interchange system, and designated in such a system as a drug imported pursuant to this part.

(b) The Importer may make entry for consumption and arrival of shipments containing eligible prescription drugs only at the CBP port of entry authorized by FDA to import eligible prescription drugs under section 804 of the Federal Food, Drug, and Cosmetic Act. The Importer must keep the product at a designated secured warehouse, and under appropriate environmental conditions to maintain the integrity of the products, until FDA issues an admissibility decision. The secured warehouse must be within 30 miles of the authorized Port of Entry for examination.

(c) If the entry for consumption is filed in ACE before the testing and relabeling of the eligible prescription drug, the Importer must submit an application to bring the drug into compliance and must relabel and test the drug in accordance with the plan approved by FDA pursuant to §§ 1.95 and 1.96 of this chapter.

(d) Upon arrival in the United States of an initial shipment that contains a batch of an eligible prescription drug identified in a Pre-Import Request that has been granted by FDA, the Importer must select a statistically valid sample of that batch to send to a qualifying laboratory for Statutory Testing, unless the manufacturer conducts the Statutory Testing at a qualifying laboratory.

(1) In the case of any subsequent shipment composed entirely of a batch of an eligible prescription drug that has already been tested in accordance with this part, the Importer must

select a statistically valid sample of the shipment to send to a qualifying laboratory for Statutory Testing.

(2) The Importer must send three sets of the samples sent to the qualifying laboratory in accordance with § 251.16 to the FDA field lab identified by FDA when the Agency granted the Pre-Import Request.

(3) The Importer must submit to FDA a complete set of laboratory records, a detailed description of the selection method for the sample of the eligible prescription drug sent to the qualifying laboratory, the testing methods used, complete data derived from all tests necessary to ensure that the eligible prescription drug meets the specifications of the FDA-approved drug that are established in the NDA or ANDA, a complete Certificate of Analysis, and all relevant documentation demonstrating that the testing meets the requirements under section 804(e)(1) of the Federal Food, Drug, and Cosmetic Act, as well as any additional information FDA deems necessary to evaluate whether the drug meets manufacturing, quality, and safety standards.

(e) If the manufacturer conducts the Statutory Testing, upon arrival in the United States of an initial shipment that contains a batch of an eligible prescription drug identified in a Pre-Import Request that has been granted by FDA, the manufacturer must select a statistically valid sample of that batch to send to a qualifying laboratory for the Statutory Testing.

(1) In the case of any subsequent shipment composed entirely of a batch or batches of an eligible prescription drug that has already been tested in accordance with this part, the manufacturer must select a statistically valid sample of that shipment to send to a qualifying laboratory for that Statutory Testing.

(2) The manufacturer must send three sets of the samples the manufacturer sent to the qualifying laboratory in accordance with § 251.16 to the FDA field lab identified by FDA when the Agency granted the Pre-Import Request.

(3) The manufacturer must submit to FDA, directly in electronic form to the ESG or to an alternative transmission point identified by FDA, a complete set of laboratory records, a detailed description of the selection method for the sample of the eligible prescription drug sent to the qualifying laboratory, the testing methods used, complete data derived from all tests necessary to ensure that the eligible prescription drug meets the conditions in the FDA-approved drug's NDA or ANDA, a complete Certificate of Analysis, and all relevant documentation demonstrating that the testing meets the requirements under section 804(e)(1) of the Federal Food, Drug, and Cosmetic Act, as well as any additional information FDA deems necessary to evaluate whether the drug meets manufacturing, quality, and safety standards.

(f) After FDA has reviewed the testing results provided by the Importer or manufacturer and determined that they are acceptable, FDA will notify the Importer and then the Importer must cause the eligible prescription drug to be relabeled with the required U.S. labeling.

(g) After the eligible prescription drug has been shown by testing and relabeling to meet the requirements of section 804 of the Federal Food, Drug, and Cosmetic Act and this part, the Importer or the manufacturer must provide the written certification described in section 804(d)(1)(K) of the Federal Food, Drug, and Cosmetic Act to FDA.

§ 251.18 Post-importation requirements.

(a) *Stopping importation.* If at any point a SIP Sponsor determines that a drug, manufacturer, Foreign Seller, Importer, qualifying laboratory, or other participant in or element of the supply chain in the authorized SIP does not in fact meet all applicable requirements of the

Federal Food, Drug, and Cosmetic Act, FDA regulations, and the authorized SIP, the SIP Sponsor immediately must stop importation of all drugs under the SIP, notify FDA, and demonstrate to FDA that importation has in fact been stopped.

(b) *Field alert reports.* Importers must submit NDA and ANDA field alert reports, as described in §§ 314.81(b)(1) and 314.98 of this chapter, to the manufacturer and to FDA.

(c) *Additional reporting requirements for combination products.* For combination products containing a device constituent part, Importers must submit the reports to the manufacturer and to FDA described in § 4.102(c)(1) of this chapter and maintain the records described in §§ 4.102(c)(1) and 4.105(b) of this chapter.

(d) *Adverse event and medication error reports.* (1) *Scope.* An Importer must establish and maintain records and submit reports to FDA and the manufacturer of all adverse events and medication errors associated with the use of their drug products imported under this part.

(2) *Review of safety information.* The Importer must promptly review all domestic safety information for the eligible prescription drugs obtained or otherwise received by the Importer.

(3) *Expedited ICSRs.* The Importer must submit expedited ICSRs for each domestic adverse event or medication error to FDA and the manufacturer as soon as possible but no later than 15 calendar days from the date when the Importer has both met the reporting criteria described in this paragraph (d) and acquired a minimum data set for that adverse event or medication error.

(i) *Serious, unexpected adverse events.* The Importer must submit expedited ICSRs for domestic adverse events reported to the Importer spontaneously (such as reports initiated by a patient, consumer, or healthcare professional) that are both serious and unexpected, whether or not the Importer believes the events are related to the product.

(ii) *Other adverse event reports to be expedited upon notification by FDA.* Upon notification by FDA, the Importer must submit as expedited ICSRs any adverse event reports that do not qualify for expedited reporting under paragraph (d)(3)(i) of this section. The notice will specify the adverse events to be reported and the reason for requiring the expedited reports.

(iii) *ICSRs for medication errors.* The Importer must submit an expedited ICSR for each domestic medication error. If the report also involves one or more adverse events, the Importer must comply with all adverse event reporting requirements in this section and submit one ICSR describing both the medication error and the adverse event(s).

(4) *Followup reports for expedited ICSRs.* The Importer must actively seek any missing data elements under paragraph (d)(7) of this section or updated information for any previously submitted expedited ICSR under paragraph (d)(3) of this section. The Importer must also investigate any new information it obtains or otherwise receives about previously submitted expedited ICSRs. The Importer must submit followup reports for expedited ICSRs to FDA and the manufacturer, as soon as possible, but no later than 15 calendar days after obtaining the new information. The Importer must document and maintain records of their efforts to obtain missing or incomplete information.

(5) *Nonexpedited ICSRs.* The Importer must submit an ICSR for each domestic adverse event not reported under paragraph (d)(3)(i) of this section (all serious, expected and nonserious adverse drug experiences) to FDA and the manufacturer within 90 days from the date when the Importer has both met the reporting criteria described in this paragraph (d) and acquired a minimum data set for that adverse event.

(6) *Completing and submitting safety reports.* This paragraph (d)(6) describes how to complete and submit expedited ICSRs required under this section. Additionally, upon written

notice, FDA may require the Importer to submit any of this section's adverse event and medication error safety reports at a different time period than identified in other paragraphs.

(i) *Electronic format for submissions.* (A) ICSR and ICSR attachments must be submitted in an electronic format that FDA can process, review, and archive, as described in § 314.80(g)(1) of this chapter.

(B) The Importer may request, in writing, a temporary waiver of the requirements in paragraph (d)(6)(i)(A) of this section, as described in § 314.80(g)(2) of this chapter. These waivers will be granted on a limited basis for good cause shown.

(ii) *Completing and submitting ICSRs.*

(A) *Single submission.* Submit each ICSR only once.

(B) *Labeling.* Each ICSR must be accompanied by a copy of the current U.S. labeling as an ICSR attachment unless it is already on file at FDA as part of the SIP.

(C) *Separate ICSR.* The Importer must submit a separate ICSR for:

(1) Each patient who experiences an adverse event reportable under paragraphs (d)(3)(i) or (ii), (d)(4), or (d)(5) of this section.

(2) Each medication error reportable under paragraph (d)(3)(iii) of this section. For reports that include both a medication error and an adverse event, the Importer need only submit one ICSR describing both the medication error and the adverse event.

(D) *Coding terms.* The adverse event and medication error terms described in the ICSR must be coded using standardized medical terminology.

(E) *Minimum data set.* All ICSRs submitted under this section must contain at least the minimum data set appropriate to the type of report (adverse event or medication error). The Importer must actively seek the minimum data set in a manner consistent with its written

procedures under paragraph (d)(9) of this section. The Importer must document and maintain records of their efforts to obtain the minimum data set.

(F) *ICSR elements.* The Importer must complete all available elements of an ICSR as specified in paragraph (d)(7) of this section.

(1) The Importer must actively seek any information needed to complete all applicable elements, consistent with their written procedures under paragraph (d)(9) of this section.

(2) The Importer must document and maintain records of their efforts to obtain the missing information.

(G) *Supporting documentation.* When submitting supporting documentation for expedited ICSRs of adverse events, the Importer must:

(1) Submit for each ICSR for a domestic adverse event, if available, a copy of the autopsy report if the patient died, or a copy of the hospital discharge summary if the patient was hospitalized. The Importer must submit each document as an ICSR attachment. The ICSR attachment must be submitted either with the initial ICSR or no later than 15 calendar days after obtaining the document.

(2) Include in the ICSR a list of available, relevant documents (such as medical records, laboratory results, death certificates) that are held in their drug product safety files. Upon written notice from FDA, the Importer must submit a copy of these documents within 5 calendar days of the FDA notice.

(7) *Information reported on ICSRs.* ICSRs must include the following information:

(i) Patient information, which includes:

(A) Patient identification code;

(B) Patient age at the time of adverse event or medication error, or date of birth;

- (C) Patient gender; and
- (D) Patient weight.
- (ii) Adverse event or medication error.
 - (A) Outcome attributed to adverse event or medication error;
 - (B) Date of adverse event or medication error;
 - (C) Date of ICSR submission;
 - (D) Description of adverse event or medication error (including a concise medical narrative);
 - (E) Adverse drug event or medication error terms(s);
 - (F) Description of relevant tests, including dates and laboratory data; and
 - (G) Other relevant patient history, including preexisting medical conditions.
- (iii) Suspect medical product(s), which includes:
 - (A) Name;
 - (B) Dose, frequency, and route of administration used;
 - (C) Therapy dates;
 - (D) Diagnosis for use (indication);
 - (E) Whether the product is a combination product;
 - (F) Whether adverse event abated after drug use stopped or dose reduced;
 - (G) Whether adverse event reappeared after reintroduction of drug;
 - (H) Lot number;
 - (I) Expiration date;
 - (J) NDC; and
 - (K) Concomitant medical products and therapy dates.

(iv) Initial reporter information.

(A) Name, address, and telephone number;

(B) Whether the initial reporter is a healthcare professional; and

(C) Occupation, if a healthcare professional.

(v) Importer information, which includes:

(A) Importer name and contact office address;

(B) Importer telephone number;

(C) Date the report was received by the Importer;

(D) Whether the ICSR is an expedited report;

(E) Whether the ICSR is an initial report or followup report; and

(F) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(8) *Recordkeeping.*

(i) For a period of 10 years from the initial receipt of information, the Importer must maintain records of information relating to adverse events and medication error safety reports under this section, whether or not submitted to FDA.

(ii) These records must include raw data, correspondence, and any other information relating to the evaluation and reporting of adverse events and medication error safety information that is obtained by the Importer.

(iii) Upon written notice by FDA, the Importer must submit any or all of these records to FDA within 5 calendar days after receipt of the notice. The Importer must permit any authorized FDA employee, at reasonable times, to access, copy, and verify its established and maintained records described in this section.

(9) *Written procedures.* The Importer must develop, maintain, and follow written procedures needed to fulfill the requirements in this section for the surveillance, receipt, evaluation, and reporting to FDA and the manufacturer of adverse events and medication error safety information, including procedures for employee training, and for obtaining and processing safety information from the Foreign Seller.

(10) *Patient privacy.* The Importer must not include in reports under this section the names and addresses of individual patients; instead, the Importer must assign a unique code for identification of the patient. The Importer must include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. The names of patients, individual reporters, healthcare professionals, hospitals, and geographical identifiers in reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

(11) *Safety reporting disclaimer.* (i) A report or information submitted by the Importer under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the Importer or by FDA that the report or information constitutes an admission that the eligible prescription drug imported under section 804 of the Federal Food, Drug, and Cosmetic Act caused or contributed to an adverse event or a medication error.

(ii) The Importer need not admit, and may deny, that the report or information submitted as described in this section constitutes an admission that the drug product caused or contributed to an adverse event or a medication error.

(e) *Drug recalls.* (1) The SIP Sponsor must establish a procedure to track the public announcements of the manufacturer of each drug they import under section 804 of the Federal

Food, Drug, and Cosmetic Act and they must also monitor FDA's recall website for recall or market withdrawal information relevant to the drugs that they import under section 804.

(2) If FDA or any participant in a SIP determines that a recall is warranted, the SIP Sponsor must effectuate the recall in accordance with its written recall plan under paragraph (e)(3) of this section.

(3) A SIP must have a written recall plan that describes the procedures to perform a recall of the product and specifies who will be responsible for performing the procedures. The recall plan must cover recalls initiated by FDA, recalls initiated by the Foreign Seller or by the Importer, and recalls initiated by a drug's manufacturer, with which the Foreign Seller and/or Importer must cooperate. The recall plan must include sufficient procedures for the SIP to:

- (i) Immediately cease distribution of the drugs affected by the recall;
- (ii) Directly notify consignees of the drug(s) included in the recall, including how to return or dispose of the recalled drugs;
- (iii) Specify the depth to which the recall will extend (e.g., wholesale, intermediate wholesale, retail or consumer level);
- (iv) Notify the public about any hazard(s) presented by the recalled drug when appropriate to protect the public health;
- (v) Conduct effectiveness checks to verify that all consignees at the specified recall depth have received notification about the recall and have taken appropriate action;
- (vi) Appropriately dispose of recalled product; and
- (vii) Notify FDA of the recall.

(4) In the event of a recall, Importers and Foreign sellers must, upon request by FDA, provide transaction history, information, and statement (as these terms are defined in sections 581(25), 581(26), and 581(27) of the Federal Food, Drug, and Cosmetic Act).

§ 251.19 Reports to FDA.

(a) A SIP Sponsor must submit a report to FDA each quarter containing the information set forth in this section, beginning after the SIP Sponsor files an electronic import entry for consumption for its first shipment of drugs under the SIP. If the SIP Sponsor specifies in such report that the information contained in the report is being transmitted on behalf of the Importer and in order to fulfill the Importer's obligation under § 251.12, the Importer need not separately submit such information to FDA.

(b) The report must contain the following information:

(1) The name, address, telephone number, and professional license number (if any) of the Importer;

(2) The name and quantity of the active ingredient of the imported eligible prescription drug(s);

(3) A description of the dosage form of the eligible prescription drugs;

(4) The date(s) on which the eligible prescription drug(s) were shipped;

(5) The quantity of the eligible prescription drug(s) that was shipped;

(6) The lot or control number assigned to the eligible prescription drug(s) by the manufacturer of the eligible prescription drug(s);

(7) The point of origin (i.e., the manufacturer) and the destination (i.e., the wholesaler, pharmacy, or patient to whom the Importer sells the drug) of the eligible prescription drug(s);

(8) The per unit price paid by the Importer for the prescription drug(s) in U.S. dollars;
and

(9) Any other information that FDA determines is necessary for the protection of the public health.

(c) The Importer must also confirm that the eligible prescription drugs was bought directly from the manufacturer by the Foreign Seller and that the Foreign Seller sold the eligible prescription drug(s) directly to the Importer.

(d) The report must include the following documentation:

(1) Documentation from the Foreign Seller specifying the manufacturer of each eligible prescription drug and the quantity of each lot of the eligible prescription drug(s) received by the Foreign Seller from that manufacturer;

(2) Documentation demonstrating that the eligible prescription drug was received by the Foreign Seller from the manufacturer and subsequently shipped by the Foreign Seller to the Importer;

(3) Documentation of the quantity of each lot of the eligible prescription drug(s) received by the Foreign Seller demonstrating that the quantity being imported into the United States is not more than the quantity that was received by the Foreign Seller;

(4) Documentation demonstrating that the sampling and testing requirements described in section 804(d)(1)(J)(i)(III) of the Federal Food, Drug, and Cosmetic Act were met for each shipment of each eligible prescription drug.

(e) The report must include certifications from the Importer for each shipment of each eligible prescription drug that the drug is approved for marketing in the United States and is not

adulterated or misbranded and meets all labeling requirements under the Federal Food, Drug, and Cosmetic Act. This certification must include:

(1) That there is an authorized SIP.

(2) That the imported drug is covered by the authorized SIP.

(3) That the drug is an eligible prescription drug as defined in this part.

(4) That the FDA-approved counterpart of the drug is currently commercially marketed in the United States.

(5) That the drug is approved for marketing in Canada.

(6) That the drug is not adulterated or misbranded and meets all labeling requirements under the Federal Food, Drug, and Cosmetic Act.

(f) The report must include laboratory records, including complete data derived from all tests necessary to ensure that each eligible prescription drug is in compliance with established specifications and standards, and documentation demonstrating that the Statutory Testing was conducted at a qualifying laboratory, unless the manufacturer conducted the testing and submitted this information directly to FDA.

(g) The report must include data, information, and analysis on the SIP's cost savings to the American consumer for the drugs imported under the SIP.

§ 251.20 Severability.

The provisions of this part are not separate and are not severable from one another. If any provision is stayed or determined to be invalid, the remaining provisions shall not continue in effect.

§ 251.21 Consequences for violations.

(a) An article that is imported or offered for import into the United States in violation of section 804 of the Federal Food, Drug, and Cosmetic Act or this part is subject to refusal under section 801 of the Federal Food, Drug, and Cosmetic Act.

(b) The importation of a prescription drug in violation of section 804 of the Federal Food, Drug, and Cosmetic Act, the falsification of any record required to be maintained or provided to FDA under such section, or any other violation of this part is a prohibited act under section 301(aa) of the Federal Food, Drug, and Cosmetic Act.

Dated: December 11, 2019.

Brett P. Giroir,

Acting Commissioner of Food and Drugs.

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