



March 2, 2023

Kim Bimestefer, Executive Director
Colorado Department of Health Care Policy & Financing
1570 Grant Street
Denver, CO 80203

Re: Colorado's Section 804 Importation Program Proposal

Dear Executive Director Bimestefer,

This letter responds to the Section 804 Importation Program (SIP) Proposal that was submitted by the Colorado Department of Health Care Policy & Financing on December 5, 2022.

FDA welcomes your interest in pursuing a SIP and appreciates the efforts you have made to seek authorization of your proposal. Consistent with the July 2021 Executive Order on Promoting Competition in the American Economy, FDA is committed to working with States such as Colorado and Indian Tribes that propose to develop SIPs under section 804 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the final rule on Importation of Prescription Drugs (see 85 FR 62094; 21 CFR part 251). To assist you with this process, and pursuant to 21 CFR 251.4(c)(1), FDA has identified information that was not provided in your submission but is required pursuant to the final rule. This information was identified after an evaluation of the completeness of your SIP proposal. Additional information may be identified, for example related to your proposals for demonstrating cost savings, after FDA conducts a full evaluation of your SIP proposal. In particular, your proposal did not include the information noted below. You may add the required information to your current SIP proposal or submit a new SIP proposal. We look forward to continuing to work with you toward our shared goal of achieving a significant reduction in the cost of prescription drugs to the American consumer without posing additional risk to the public's health and safety.

Information Missing from the Overview of the SIP Proposal:

- 251.3(d)(5) Provide the name and address of the manufacturer of the finished dosage form of each eligible prescription drug listed on the Drug List, if known or reasonably known.
- 251.3(d)(6) Provide the name and address of the manufacturer of the active ingredient or ingredients of the eligible prescription drugs, if known or reasonably known.
- 251.3(d)(10) Provide adequate evidence of registration for the relabeler, to include a business operation of 'relabel' as required under 21 CFR 207.25(f).



Information Missing from the Importation Plan:

- 251.3(e)(1) Identify the manufacturer(s) of the finished dosage form and the active ingredient or ingredients of each eligible prescription drug that the SIP Sponsor seeks to import, if known or reasonably known.
 - Clarify whether the names and addresses in Appendix D, Drug List with Required Data Elements, are for the manufacturer of the finished dosage form of the eligible prescription drug.
- 251.3(e)(6) Provide adequate evidence that each HPFB-approved drug's FDA-approved counterpart drug is currently commercially marketed in the United States. We recommend, at a minimum, including information showing that each drug product is listed in the Active Section of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book.
- 251.3(e)(14) Include an explanation of how the SIP Sponsor will ensure that product that is returned after distribution in the United States is properly dispositioned in the United States, if it is a non-saleable return, in order to protect patients from expired or unsafe drugs, and an explanation of how the SIP Sponsor will prevent the non-saleable returned eligible prescription drugs from being exported from the United States. Describe:
 - How the importer or designee will ensure non-saleable returned products are properly dispositioned in the United States.
 - How non-saleable returned products will be removed from the pharmaceutical distribution supply chain.
- 251.3(e)(15)(vi) Include the adoption of processes and procedures for uncovering and addressing conflicts of interest.
- 251.9(a) Any Foreign Seller(s) designated in a SIP Proposal must be registered with FDA before FDA will authorize the SIP Proposal. Ensure that the proposed Foreign Seller is registered with a business operation 'SIP Foreign Seller'. Please contact edrls@fda.hhs.gov for questions and assistance with registration.

Information on the Eligible Prescription Drugs:

- 251.3(e)(11)(i) 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 storage, handling, and distribution practices of supply chain participants, including transportation providers, meet the requirements of 21 CFR part 205 (requirements for state licensing of wholesale prescription drug distributors) and do not affect the quality or impinge on the security of the eligible prescription drugs.
 - For sterile drugs or drugs that require special storage conditions such as temperature control, please explain how the SIP Sponsor 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.

Information on the Proposed Labeling:

- 251.3(e)(8) Include a copy of the FDA-approved drug labeling for the FDA-approved counterpart 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 the Prescribing Information, carton and container labeling, and patient labeling (e.g., Medication Guide, Instructions for Use, patient package inserts), with all differences annotated and explained. The SIP Proposal must also include a copy of the HPFB-approved labeling.
 - Ensure that this side-by-side comparison of the FDA-approved labeling and the proposed labeling is provided for each drug identified in the SIP Proposal.
 - Ensure that all approved and proposed labeling is provided in the SIP Proposal including all the carton and container labeling.
 - If your SIP Proposal does not include all the package sizes available for the FDA-approved counterpart, then please revise the HOW SUPPLIED/STORAGE AND HANDLING section of the proposed Prescribing Information (PI) to delete package sizes that are not being proposed for importation.
 - Ensure that your proposed labeling is based on the most recent version of the FDA-approved labeling.
 - The FDA-approved labeling for the NDA drug products can be found on Drugs@FDA. If such labeling is not available on Drugs@FDA, you may be able to obtain the labeling from the manufacturers. You can also obtain it through a Freedom of Information Act (FOIA) request.
 - The FDA-approved labeling for ANDA drug products is typically not posted on Drugs@FDA. The labeling for FDA-approved ANDA drug products can be obtained through a FOIA request. You may also be able to obtain it from the manufacturers.
 - The revision date should match the revision date of the latest FDA-approved labeling.
- 251.13(b)(4) At the time the drug is sold or dispensed, the labeling of the drug must be the same as the FDA-approved labeling under the applicable NDA or ANDA, with certain exceptions. An eligible prescription drug's labeling can only deviate from the FDA-approved labeling in the ways listed at 251.13(b)(4)(i)-(vii). Ensure that the content and format of the container and carton labeling of each eligible prescription drug included in the SIP Proposal is the same as the FDA-approved carton and container labeling.
- 251.13(b)(4)(i) The Importer's NDC for the eligible prescription drug must replace any NDC appearing on the label of the FDA-approved drug.



- 251.13(b)(4)(iii) The labeling must bear conspicuously, among other things, the name and place of business of the Importer.
 - We recommend you add the Importer's name and place of business at the end of the PI in addition to the HOW SUPPLIED/STORAGE AND HANDLING section. We also recommend you add the Importer's information at the end of the Medication Guide, Instructions for Use, and/or patient package inserts.
 - The statement of the place of business should include the street address, city, state, and ZIP Code. The street address can be omitted if it is shown in a current city directory or telephone directory. If the importer's street address is not shown in a current city directory or telephone directory, the street address of the importer should be added.
 - The Importer may submit to FDA a supplemental proposal to modify the labeling of an eligible prescription drug, for example if the eligible prescription drug's container is too small to fit the additional required information, in accordance with 251.13(d).
- Consistent with 21 CFR 251.13(c), provide the written procedure for the relabeling process of your proposed imported prescription drugs.
 - If it is not possible to relabel a product without affecting the container closure system, such as a blister pack, then the product cannot be imported under a SIP as per the rule. The final rule does not allow repackaging of drugs that breaches the container closure system, such as a blister pack, which could introduce unnecessary risk of adulteration, degradation, and fraud for drugs imported under a SIP. The final rule also does not permit affixing a conforming label to the outside of the container closure system in lieu of relabeling the immediate container of the product. For example, Farxiga (Forxiga in Canada) tablets listed in the Drug List are packaged in blister packs according to the HPFB-approved labeling. If relabeling the drug product would require breaching the container closure system (e.g., breaking the foil on a blister pack), then the product cannot be imported under a SIP.

Please indicate by April 7, 2023, if you intend to provide the additional required information or if you would like to withdraw the current submission and potentially resubmit it at a later time. If you do not respond by the above date indicating your intention to respond to this request, we will conclude our review of the December 2022 proposal and deny authorization of that submission.

If you submit additional or revised information to the SIP Proposal, please describe the changes that have been made since your previous submission. Please submit any questions, requests to meet, or any revisions to your SIP Proposal for agency review to:

SIPDrugImportsandRFP@fda.hhs.gov.



Additional Comments:

In the December 2022 proposal, you requested additional information on (1) FDA's SIP proposal review process; (2) standards on demonstrating cost savings; and (3) flexibility on the list of eligible prescription drugs that may be imported under an approved SIP. In March 2022, FDA held a meeting with representatives from several states, the National Academy for State Health Policy, and the U.S. Department of Health and Human Services to discuss the development of Section 804 Importation Program proposals. FDA's presentation on "Section 804 Importation Program: Overview of Final Rule and Implementation" and HHS's presentation on "Projecting Cost Savings for the American Consumer" are available on FDA's website at <https://www.fda.gov/about-fda/reports/importation-drugs-originally-intended-foreign-markets>. In May 2022, FDA issued guidance titled *Importation of Prescription Drugs Final Rule Questions and Answers*, which is intended to summarize in plain language the legal requirements in the final rule.

Your SIP Proposal indicates that imported medications will enter through the port of entry located in Buffalo, New York. The final rule specifies that entry and arrival of a shipment containing an eligible prescription drug is limited to the U.S. Customs and Border Protection (CBP) port of entry authorized by FDA; see 21 CFR 251.17(b). At this time, the only port of entry that has been authorized by FDA is located in Detroit, Michigan. See, FDA Supplemental Guide for the Automated Commercial Environment/International Trade Data System (ACE/ITDS), at <https://www.cbp.gov/document/guidance/fda-supplemental-guide> (p. 16).

With regard to the prescription drugs that you may seek to import, we note that some of the drug products in your SIP Proposal may not be "eligible prescription drug[s]" as defined in 21 CFR 251.2. Under 21 CFR 251.2, the Canadian drug product must "meet[] the conditions in an FDA-approved new drug application (NDA) or abbreviated new drug application (ANDA) for a drug that is currently commercially marketed in the United States, including those relating to the drug substance, drug product, production process, quality controls, equipment, and facilities." The Canadian varenicline drug product in Appendix G appears to have a different manufacturer, inactive ingredients, tablet characteristics, and storage and handling conditions than the varenicline drug product that is presented as its FDA-approved counterpart. To give another example, the Canadian Pulmicort Turbuhaler products listed in Appendix D appear to have different strengths and different inactive ingredients than the Pulmicort Flexhalers that are presented as their FDA-approved counterparts.

We also note that it may be more efficient to gather information only for the eligible prescription drug product(s) identified in your SIP Proposal that you intend to include in an initial Pre-Import Request. Accordingly, you may choose to submit information for a smaller selection of drug products. FDA can then evaluate the information about this smaller selection of drug products and you may submit a supplemental proposal to add eligible prescription drugs at a later time.

The December 2022 proposal additionally indicates that you intend to work directly with manufacturers and that manufacturers will authorize eligible prescription drugs to be included in your importation program. If a drug that was originally intended to be marketed in a foreign country is authorized by its manufacturer to be marketed in the U.S., and if the manufacturer



“cause[s] the drug to be labeled to be marketed in the [U.S.],” the drug may be imported under section 801 of the FD&C Act, rather than under section 804. There is information on manufacturer-authorized importation of drugs originally intended to be marketed in a foreign country in our guidance *Importation of Certain FDA-Approved Human Prescription Drugs, Including Biological Products, and Combination Products under Section 801(d)(1)(B) of the Federal Food, Drug, and Cosmetic Act*.

We note that the protections that are set forth in section 804 and 21 CFR part 251, including those related to the establishment of a SIP and to foreign sellers, importers, labeling, supply chain security, and laboratory testing, are necessary to ensure that importation of eligible prescription drugs without the manufacturer’s authorization poses “no additional risk to the public’s health and safety.” Likewise, the provisions in the statute and the regulation that place requirements on manufacturers, for example, the requirement in section 804(h) that the manufacturer give the importer “written authorization” for the importer to use a drug’s approved labeling, are necessary because the importation is occurring without the manufacturer’s authorization. As you point out, 21 CFR 251.13(b)(4)(iv) requires that the labeling of a drug imported by a SIP bear a statement indicating that the product was imported without the manufacturer’s authorization. The preamble to the final rule promulgating 21 CFR part 251 explains that this “will help to prevent potential misperceptions regarding whether the manufacturer authorized the product to be imported.” (85 Fed. Reg. 62094, 62105 (Oct. 1, 2020)). We would be happy to discuss further with you details about your planned outreach to manufacturers, in order to discern the extent to which the importation would occur with the manufacturer’s authorization.

Sincerely,

S. Leigh Verbois, PhD
Director
Office of Drug Security, Integrity & Response
Office of Compliance
Center for Drug Evaluation and Research