December 20, 2024

Kim Bimestefer, Executive Director
Colorado Department of Health Care Policy & Financing
303 E 17th Avenue
Denver, CO 80203

Re: Colorado Department of Health Care Policy & Financing Section 804 Importation Program Proposal

Dear Executive Director Bimestefer:

This letter responds to the Section 804 Importation Program (SIP) proposal that was initially submitted by the Colorado Department of Health Care Policy & Financing to the Food and Drug Administration (FDA) on December 5, 2022, and subsequently revised on February 27, 2024, and August 28, 2024.

Consistent with the July 2021 Executive Order on Promoting Competition in the American Economy, FDA is committed to continuing to work with states, such as Colorado, and Tribes that propose to develop Section 804 Importation Programs (SIPs) in accordance with section 804 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA's implementing regulations. To assist you with this process, numerous subject matter experts at FDA and other components of the Department of Health and Human Services (HHS) have carefully and thoroughly reviewed your revised SIP proposal and prepared this letter. FDA has found the items listed below do not meet the requirements in 21 CFR Part 251, which are necessary for a sponsor to demonstrate a SIP meets the statutory obligation to ensure that importation under section 804 of the FD&C Act will reduce the cost of covered products to the American consumer without posing additional risk to the public's health and safety.

Below is a summary of deficiencies identified during FDA's review of this SIP proposal. Specifically, FDA notes:

1. The SIP proposal does not adequately describe how the SIP sponsor will ensure drug supply chain security for products imported under the SIP. Section 251.3(e)(11)(ii) requires the SIP proposal to describe the procedures the SIP Sponsor will use to ensure the supply chain is secure.

    a. Currently, there is insufficient detail describing the Importer's plan to comply with section 251.14(d)(2), which requires the Importer to facilitate the affixation or imprinting of a product identifier, as defined in section 581(14) of the FD&C Act, to all eligible prescription drugs. The SIP proposal provides that the relabeler will "relabel with FDA Required/US labeling standards on behalf of the Colorado Importer, including Drug Supply Chain Security Act (DSCSA)-required product identifier…", but the SIP proposal

and Importer's standard operating procedure (SOP) covering relabeling do not provide sufficient detail regarding the firm's relabeling plans, nor do they reflect a precise and complete understanding of the components of a DSCSA-compliant product identifier. Specifically, SOP-804-006 notes that drug labeling must contain, among many other items, the National Drug Code, lot number, and expiration date of the product. The SOP also mentions that the relabeler must "facilitate the affixation or imprinting of a Unique Product Identifier (UPI) for all eligible prescription drugs." However, the SOP does not reference or adequately describe procedures to ensure compliance with the following:

i. The section 251.14(d)(2) requirement to affix or imprint a product identifier to eligible prescription drugs. The SOP should include procedures describing how the product will be relabeled with the product identifier.
ii. The section 581(20) of the FD&C Act requirement for the product identifier to contain a unique alphanumeric serial number of up to 20 characters. Although the SOP references a UPI, it does not provide sufficient detail describing the data elements that would comprise the UPI or indicate that the UPI will satisfy the serial number requirement.
iii. The section 581(14) requirement for the product identifier to be affixed or imprinted in both human- and machine-readable formats.

2. The SIP proposal does not adequately describe your pharmacovigilance plan or how the Importer will manage adverse event reporting. Section 251.3(d)(11)(iv) requires a summary of how the SIP Sponsor will ensure compliance with post-importation pharmacovigilance and other requirements of the FD&C Act and part 251. Section 251.3(e)(11)(iv) requires the SIP proposal to include the steps that will be taken to ensure the Importer fulfills its responsibilities to submit adverse event, field alert, and other reports required by the SIP, FD&C Act, or part 251.

   a. Provide written procedures on how the Importer will submit Individual Case Safety Reports (ICSRs) to FDA and to manufacturers for all eligible prescription drugs imported under your SIP, including combination products in accordance with section 251.18(c) and 4.102(c)(1). Although the SIP proposal states the proposed drug list does not include any combination products, Spiriva Respimat, Ozempic, and Victoza are combination products. The SIP proposal should include reporting procedures for combination products.

   b. The SIP proposal does not provide adequate details regarding procedures for Rocky Mountain Poison and Drug Safety (RMPDS), which will be responsible for all FDA-required adverse event reporting and for responding to consumer inquiries. Specifically, the SIP proposal should address how RMPDS will: 1) assess seriousness; 2) assess expectedness; and 3) report adverse drug event information to the manufacturer. It is recommended that the Importer provide RMPDS with the labeling FDA has authorized for each eligible prescription drug. Without the product labeling, it is not clear how RMPDS can assess expectedness, or fulfill any of the pharmacovigilance requirements under part 251.

c. In addition, the SIP proposal describes the submission of ICSRs to FDA through the Safety Reporting Portal in the summary of the pharmacovigilance activities that RMPDS will undertake, while in Table 12 the proposal states that submission will be via the E2B database. The proposal should be consistent regarding the procedures specified for reporting ICSRs to FDA. The proposal should provide procedures for how RMPDS will ensure that the surveillance, receipt, evaluation and reporting to FDA and the manufacturer of adverse event information is done in accordance with section 251.18(d)(9).

3. Section 251.3(d)(9) and (10) require that the overview of the SIP proposal must include the name and address of the Importer and of the FDA-registered repackager or relabeler, if different than the Importer. Although your SIP Proposal indicates that the Importer will relabel the eligible prescription drugs at a location in Boise, ID, Appendix F lists a Perrysville, OH location where relabeling could potentially occur. It is unclear if this location is intended for relabeling. Please clarify the use, if any, of this location.

4. Section 251.3(e)(11)(i) requires a description of the procedures the SIP Sponsor will use to ensure the storage, handling, and distribution practices of supply chain participants, including transportation providers, meet the requirements of 21 CFR part 205 (“Guidelines for State Licensing of Wholesale Prescription Drug Distributors”) and do not affect the quality or impinge on the security of the eligible prescription drugs. 21 CFR 251.13(c) requires that relabeling meet applicable requirements including current good manufacturing practice requirements in 21 CFR parts 210 and 211.

   a. For sterile drugs, or drugs that require special storage conditions, 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.

      i. Clarify how relabeling will be feasible for drugs that need to be in refrigerated conditions (e.g., Ozempic and Victoza) while ensuring stability.
      ii. Clarify how relabeling will be feasible for sterile injection pens (e.g., Ozempic and Victoza) while controlling contamination and preserving sterility.

5. Section 251.13(c) provides that the Importer is responsible for relabeling the drug, or arranging for it to be relabeled, to meet the requirements of part 251. The relabeling and associated limited repackaging activities must meet applicable requirements, including applicable current good manufacturing practice requirements under parts 210 and 211.

   a. 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. Part 251 does not allow repackaging of drugs that breaches the container closure system, such as a blister pack, which would introduce unnecessary risk of adulteration, degradation, and fraud for drugs imported under a SIP. Part 251 also does not permit affixing a conforming label to the outside of a drug product’s packaging in lieu of relabeling the immediate container of the product.

i. Ibrance and Trikafta are packaged in blister packs or dose packs. If relabeling these drug products would require breaching their container closure systems (e.g., breaking the foil on a blister pack), then these products cannot be imported under a SIP.

ii. Confirm that these products can be relabeled without breaching the container closure system. If not, remove any such drugs from the SIP proposal.

b. For Spiriva Respimat Inhalation Spray, it is not clear how it could be relabeled without potentially affecting the safety and effectiveness of the product. For example, there is minimal clearance between the outer surface of the labeled cartridge and the internal spring of the device. As the spring moves relative to the cartridge with use of the device, there is potential for interference if the thickness of the replaced labeling is greater than the space tolerance between those two components . We also note that the label includes dose markings, which means its placement is critical to the product's safe and effective use. If you would like us to continue to consider the inclusion of this drug in your SIP, explain how you would relabel the cartridges without potentially affecting the performance and reliability of the product.

Additional Notes

The labeling corrections attached to this Request for Information (RFI) do not necessarily constitute all changes that may be required to the labeling of an eligible drug imported under the SIP. FDA will review your SIP proposal and consider it for authorization without conducting its final review of the labeling of the drugs you propose to import. In the event your SIP proposal is authorized, FDA will make a final determination regarding the labeling for the eligible prescription drugs you intend to import when it considers a Pre-Import Request for those drugs. We recommend that you submit corrected and up-to-date labeling after you have purchased the drugs from your Foreign Seller, and before you submit your Pre-Import Request.

Additionally, we note that for potential revisions to the SIP proposal before authorization, particularly in response to an RFI, Colorado is encouraged to make corresponding revisions to the explanation of cost savings and supporting documentation, focusing on any changes to the SIP proposal that could result in significant changes to the cost-savings estimates. If the state has new economic data that were not available at the time the cost analysis was developed in December 2023, such as more recent utilization and cost data from the Colorado All Payers Claims Database or updated prices from the Quebec formulary, then applying that recent data would reduce the uncertainty in forecasting cost savings and would facilitate a meaningful evaluation of the cost analysis of your revised SIP proposal.

We also note that, while the SIP proposal does not include a detailed description of the Statutory Testing you propose to conduct, this does not preclude authorization of your proposal. Under section 804(d)(1)(J) and (L) and section 804(e) of the FD&C Act, drugs imported under section 804 must be tested for authenticity, for degradation, and to ensure they are in compliance with established specifications and standards. The regulations provide that a SIP proposal must "[d]escribe, 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" per section 251.3(e)(7). Thus, while your SIP proposal provides only a high-level summary of the testing that you will conduct, we presume that you have described the testing "to the extent possible."

Before you import a drug, you will need to file, and FDA will need to grant, a Pre-Import Request. Unless the manufacturer intends to conduct the Statutory Testing itself, the Pre-Import Request must describe the testing methods that will be used per section 251.5(c)(4)(xi)(C). This description must be sufficiently detailed for FDA to ensure testing meets the requirements of section 251.16(d), which provides that:

> [a] 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 and standards, which include the analytical procedures and methods and the acceptance criteria. In addition, to test for degradation, a stability-indicating assay provided by the manufacturer must be conducted on the sample of the drug that is proposed for import.

Please also note that the acceptability of the qualifying laboratory could change. If a laboratory is inspected and receives an OAI (Official Action Indicated) classification, or if the ISO 17025 accreditation for the laboratory expires, that laboratory would no longer be considered acceptable. We recommend that the state develop a plan to assure the ongoing compliance of the laboratory and a contingency plan if the laboratory is no longer acceptable.

Lastly, we suggest providing the warehouse address that is within 30 miles of the CBP port of entry in Detroit, Michigan, if available. FDA can still consider authorization of the SIP proposal prior to securing a warehouse location. However, at the time of submitting a Pre-Import Request, Colorado must specify the secure distribution facility within 30 miles of the Port of Detroit where the eligible prescription drugs will be stored.

Please indicate if you intend to provide the required information identified in this RFI. When submitting additional or revised information or a revised proposal, please describe the changes that have been made since your previous submission. Please submit any questions, requests to meet, or revisions to your SIP proposal for agency review to SIPDrugImportsandRFP@fda.hhs.gov.

Sincerely,

Sandi L. Verbois -S

Digitally signed by Sandi L. Verbois -S
Date: 2024.12.20 12:18:13 -05'00'

S. Leigh Verbois, PhD
Director
Office of Drug Security, Integrity & Response
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