UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF FLORIDA
TAMPA DIVISION

State of Florida, *et al.*,

Plaintiffs,

v.

Food and Drug Administration, *et al.*,

Defendants.

Case No. 8:22-cv-01981-TPB-JSS

Defendants' Supplemental Status Report for the APA Claim

Consistent with Defendants' August 8, 2023 Status Report, Defendants now submit this supplemental status report to "apprise the Court of [a] subsequent, relevant development[] regarding the decision-making timeline for Florida's SIP proposal." *See* ECF No. 84. Based on reviews of Florida's Section 804 Importation Program ("SIP") proposal over the past few months by FDA and HHS components, *see id.*, FDA's Office of Drug Security, Integrity, and Response ("ODSIR")—which oversees the Section 804 Importation Program—determined that Florida's proposal still does not contain certain information that is required under the SIP regulations. On August 14, 2023, ODSIR requested that Florida provide the missing information by August 28, 2023. *See* Ex. A.

The missing information relates to critical aspects of Florida's SIP

August 14, 2023

Jason Weida, Secretary
Florida Agency for Health Care Administration
2727 Mahan Drive, Mailstop 1
Tallahassee, FL 32308

Re: Florida Agency for Health Care Administration Section 804 Importation Proposal

Dear Secretary Weida:

This letter responds to the Section 804 Importation Program (SIP) proposal that was initially submitted by the Florida Agency for Health Care Administration to the Food and Drug Administration (FDA) on November 23, 2020, and subsequently revised on: April 19, 2021, September 15, 2021, November 15, 2021, and April 21, 2023.

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 Florida, and Tribes that propose to develop Section 804 Importation Programs 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 identified several deficiencies, listed below, that do not meet the requirements in 21 CFR Part 251, which are necessary for a sponsor to demonstrate that a SIP meets the statutory obligation to ensure that importation under section 804 will reduce the cost of covered products to the American consumer without posing additional risk to the public's health and safety. FDA is requesting that you provide additional or clarifying information to address the deficiencies summarized in this letter by **28 August 2023**, which will assist FDA in making a prompt decision on the SIP proposal. If the State needs more time to respond to the request, please let FDA know as soon as possible. Should FDA not receive a response, FDA will issue a decision based on Florida's pending submission. Further, we offer to meet via teleconference with SIP sponsors if any of our concerns can be further clarified as the State is compiling the requested information.

Below is a summary of deficiencies identified during FDA's review of the SIP proposal, encompassing specific information critical to agency review and pertaining to areas identified in previous Requests for Information (RFIs) as not addressed or lacking specificity. Specifically, FDA notes:

1. The SIP proposal does not adequately describe how the SIP sponsor will assure drug supply chain security for products imported under the SIP. As detailed below, the SIP proposal does not adequately describe the SIP Sponsor's plan,

pursuant to 251.14(a), for ensuring that the Foreign Seller and Importer are able to meet the requirements under 251.14(c) and (d) or describe how the returned product will be dispositioned in the United States and not exported, as required by 251.3(e)(14). Specifically:

a. The SIP proposal does not specify whether the Foreign Seller has the required systems in place for determining whether a product in its possession is a suspect foreign product or illegitimate foreign product as required in 251.14(c)(1) and (2).
b. The SIP proposal does not demonstrate that the Foreign Seller will promptly provide information about its transactions with the manufacturer and importer upon request by FDA or other appropriate Federal or State officials for the purposes of investigating a suspect foreign product or illegitimate foreign product as required by 251.14(c)(3) and (7). The SIP proposal addresses this in the context of a recalled product only.
c. It is unclear whether the Foreign Seller will, upon receiving a request for verification and determining that the section 804 serial identifier (SSI) does not correspond with the SSI affixed or imprinted by the Foreign Seller, conduct the necessary investigation into a suspect foreign product or advise of an illegitimate foreign product determination as required under 251.14(c)(5).

As noted above, FDA has specific concerns that the SIP proposal lacks clarity with respect to the Foreign Seller's plan for meeting applicable requirements for handling suspect foreign product and illegitimate foreign product, including investigating suspect and illegitimate foreign product and responding to requests for verification. As the SIP proposal acknowledges, "working with a Foreign Seller to import prescription drugs is a novel concept for the U.S. drug supply chain." The Foreign Seller would be receiving product from the original manufacturer that is not compliant with the Drug Supply Chain Security Act (DSCSA), because that product would have been intended and labeled for the Canadian market. Accordingly, Part 251 imposes important requirements on the Foreign Seller to be able to identify, investigate, and respond to requests regarding suspect foreign product and illegitimate foreign product that generally correspond to those DSCSA verification requirements imposed on a "manufacturer" in the U.S. drug supply chain under section 582(b)(4)(A) through (C) of the FD&C Act. These requirements are an important safeguard to help prevent counterfeit, diverted, stolen, or otherwise harmful drugs received by the Foreign Seller from being imported and further distributed to U.S. consumers and to help identify and trace such product found in the supply chain so that it can be investigated and removed if necessary. Ensuring that illegitimate product is not dispensed to patients in the United States is critical to protecting public health and safety.

While we acknowledge that the SIP proposal includes general assurances that the Foreign Seller will meet certain applicable requirements, such as that the State will monitor the Foreign Seller "being able to ascertain whether a shipment of Canadian prescription drugs contains suspect products, notifying the FDA of the discovery of suspect products, and having the means to quarantine said products until disposition," the information provided in the proposal, including the Foreign Seller's Standard Operating Procedures (SOPs) in Attachment I, does not clearly describe or explain how these requirements will be met. For example, while the SOPs on "Temperature Monitoring During Storage and Transportation" and "Receiving Goods" appear to describe systems and procedures through which the Foreign Seller (or their third-party logistics operator or contract manufacturing organization) would monitor certain drugs that are in its possession, these processes do not appear to specifically pertain to

meeting the requirements, including notification to FDA, detailed in 251.14(c)(1)-(3). Without an adequate level of assurance that the SIP Sponsor and the Foreign Seller not only understand the Foreign Seller's obligations with respect to handling suspect and illegitimate foreign product under 21 CFR 251.14, but also have the systems and procedures in place to adhere to these requirements, it is unclear whether the supply chain described within the SIP proposal will ensure supply chain security and patient safety.

d. The SIP proposal and supporting documents indicate the Importer will affix a product identifier that will meet the specifications of section 581 and will contain machine-readable bar code, National Drug Code (NDC), lot number, and expiration date. However, under 251.14(d)(2), the product identifier to be affixed or imprinted on the eligible prescription drugs is required to include the NDC, unique alphanumeric serial number of up to 20 characters, lot number, and expiration date, in both human and machine-readable format as defined in section 581(14) of the FD&C Act. Specifically, the description of the product identifier outlined in both the SIP proposal and supporting documents do not reference the human-readable component or serial number that must be part of the product identifier.
e. The SIP proposal does not specify whether the Importer will retain the required records to associate the product identifier with the information described in 251.14(d)(3) and (4), including the Canadian Drug Identification Number (DIN) and SSI assigned by the Foreign Seller.
f. The SIP proposal does not specify whether the Importer will, upon receipt of an eligible prescription drug and records from a Foreign Seller, compare such information with information the Importer received from the manufacturer as required by 251.14(d)(5).
g. The SIP proposal provides descriptions of expectations and general assurances for compliance with the FD&C Act and DSCSA, and discussion of the Importer's ability to capture, store, and transmit product tracing information. However, it is not clear that the Importer will meet all requirements of section 582(c) of the FD&C Act (i.e., requirements for product tracing, product identifier, verification, and authorized trading partner), including requirements that apply to subsequent transactions with trading partners.
    i. The proposal lacks documentation to demonstrate that the Importer has the necessary systems in place under the verification requirements under section 582(c) of the FD&C Act to adequately address suspect and illegitimate products.
    ii. The SIP proposal does not clearly indicate that the Importer will ensure its trading partners are authorized.

As noted above, FDA is particularly concerned that it is unclear whether (1) the product identifier as described in the SIP proposal to be affixed or imprinted on the product by the Importer would meet the requirements outlined in the definition of "product identifier" in section 581(14) of the FD&C Act, as required by 251.14(d)(2); or (2) records allowing for the association of the product identifier with the SSI assigned by the Foreign Seller, and the Canadian DIN that was on the package originally received by the Foreign Seller, will be properly maintained by the Importer, as required by 251.14(d)(3) and (4). While the proposal and one of the Importer's SOPs says that the product identifier will include a "machine-readable bar code unique to that particular lot of imported prescription drugs," and another SOP discusses application of a "serial number" or a "unique

identifier" and "re-serialization," these procedures do not clearly explain how the product identifier will conform with the DSCSA requirement that the product identifier itself be human- and machine-readable and contain a "unique alphanumeric serial number of up to 20 characters," and how the retained records will be associated with the Canadian product. The serial number is an important part of the "standardized numerical identifier," a key required feature of the product identifier under DSCSA that allows for lot-level tracing of products up to the manufacturer in a typical U.S. drug supply chain. Because the responsibility that would typically fall on a manufacturer to assign a DSCSA-compliant product identifier would not apply to eligible prescription drugs that are originally intended for the Canadian market, Part 251 imposes important requirements on the Importer to properly assign a product identifier, and maintain the proper records to associate the product identifier with the Canadian product, as a safeguard in order to match the protections of the DSCSA through other means. The product identifier provides important data elements that both allow a product to be identified and traced throughout the supply chain and provide important information to protect patient safety. Uncertainty with respect to whether the Importer will affix or imprint a product identifier that contains each element of the product identifier as defined in section 581(14) raises concerns about whether the Importer and subsequent trading partners will be able to effectively identify and trace the product imported under the SIP throughout the supply chain after it is relabeled for the U.S. market, thereby potentially putting the supply chain and patients at risk.

h. The SIP proposal does not adequately explain how the SIP Sponsor will ensure that the 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 provide an explanation of how the SIP Sponsor will prevent the non-saleable returned eligible prescription drugs from being exported from the United States per the requirements of 251.3(e)(14). FDA has concerns that Florida is proposing that final disposition could occur outside of the United States, which is not permitted under 251.3(e)(14). The SIP proposal does not specify what standards will be used for determining whether a returned product that is not subject to a recall is saleable per 251.3(e)(14).

Based on the information submitted with the SIP proposal, FDA is particularly concerned that it is unclear whether the return plan prevents the exportation of returned eligible prescription drugs. While the proposal describes a process by which the State will ensure that the Importer disposes certain recalled prescription drugs by contracting with a U.S. facility authorized to do so, references in the Importer SOPs in Attachment H to "returning merchandise to the licensed manufacturer or wholesaler from which it was acquired" introduces uncertainty about whether all eligible non-saleable returned products will in fact be dispositioned in the United States. Ensuring that returned eligible prescription drugs that have been relabeled for the U.S. market are not exported from the U.S. is an important safeguard under section 804(c)(3) of the FD&C Act to reduce opportunities for diversion and other forms of fraud. With the uncertainty as to whether the return plan would include returning product to a foreign manufacturer, we are concerned the supply chain could be compromised.

It is critical for the protection of public health that products imported under section 804 be held to the same level of drug supply chain security as products manufactured for the U.S. supply chain. While we acknowledge that the SIP proposal provides further information about the State's efforts to ensure supply chain security in response to our

November 16, 2022, RFI letter, including procedures for compliance with certain applicable requirements, the information provided does not adequately ensure that the supply chain for products to be imported under section 804 would be secure.

2. The SIP proposal does not explain how the SIP Sponsor will ensure that the SIP will result in a significant reduction in the cost to the American consumer of the eligible 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 (see 21 CFR 251.3(e)(9)). Without the requested additional information, HHS remains unable to meaningfully evaluate the relative likelihood that the SIP proposal would result in significant cost savings to the American consumer. Specifically:
    a. The SIP proposal does not report expenditure projections for each drug. Therefore, HHS cannot determine whether the drug-specific expenditure projections are consistent with the total expenditure projections. We note that Tables 4, 6 and 7 in Attachment E of the SIP proposal state that they contain drug-specific expenditure projections, but the drug-specific projections are redacted so that it is not possible for HHS to review them. The proposal states that FDA can "verify that information" by consulting the drugs' manufacturers or the Centers for Medicare and Medicaid Services (CMS). We note that CMS does not have drug-specific information on state supplemental Medicaid rebates. The SIP proposal must contain drug-specific expenditure information that accounts for both federal Medicaid rebates under the national rebate agreement and state supplemental Medicaid rebates, to the extent that such rebates apply, because a meaningful evaluation is not possible without that level of detail. 21 CFR 251.3(e)(9). We invite you to discuss with us the confidentiality concerns referred to in the proposal.
    b. The SIP proposal does not contain price and quantity projections for each drug under the Baseline Scenario and the Plan Scenario. As we explained in our November 16, 2022, RFI letter, HHS needs this information in order to confirm that "[t]he product of the price and quantity projections [is] consistent with the drug-specific expenditure projections."
    c. The SIP proposal's Table 4, Projected Two-Year Baseline Scenario, identifies several assumptions that underlie the Baseline Scenario's projections. HHS is not able to assess the reasonableness of these assumptions because the SIP proposal does not provide the specific estimates (e.g., "future utilization rate" and historic annual increases in Wholesale Acquisition Cost (WAC)) used for the Baseline Scenario's expenditure projections. Without the specific estimates, HHS is also unable to reproduce the major findings of your Baseline Scenario analysis.
    d. The cost analysis in the SIP proposal appears to focus on Medicaid, and the SIP proposal states that "Florida's Medicaid program will constitute most consumers." However, the SIP proposal does not address whether drugs proposed for importation would meet the requirements of that program. The preamble for the final rule states that "[a] SIP proposal cannot demonstrate cost savings in connection with a government program if the eligible prescription drugs to be imported under the SIP do not meet the program's requirements." We note that in September 2020, the Centers for Medicare & Medicaid Services issued guidance to States on FDA's final rule and the Medicaid drug rebate program, available at https://www.medicaid.gov/prescription-drugs/downloads/state-rel-187.pdf.

3. Per 251.3(e)(5), the SIP proposal must include as much of the information that is required by 251.5 about the Canadian Health Products and Food Branch (HPFB)-approved product and its FDA-approved counterpart as is available. This includes the name and quantity of the active ingredients, and the dosage form. All information is listed on the cover page of each drug labeling. However, the current SIP proposal does not specify if the information is referring to both the HPFB-approved product and its FDA-approved counterpart. Please clarify if all information (proprietary name, active ingredients, inactive ingredients, dosage forms) is the same for both HPFB- and FDA-approved drugs.

In addition to the missing or unclear information outlined above, we have noted additional deficiencies related to the proposal pertaining to areas identified in previous RFIs.

1. Per 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 New Drug Application (NDA) or Abbreviated New Drug Application (ANDA), with certain exceptions. However, the proposed labeling does not meet this requirement (e.g., the labeling of Biktarvy, Descovy, Dovato, Eliquis, Eucrisa, Juluca, Odefsey, Prezista, Ravicti, Rexulti, Symtuza, Vraylar, and Xtandi). Additionally, the SIP proposal did not provide the FDA-approved labeling or the proposed labeling for some of the drugs (e.g., Eucrisa, Odefsey, and Ravicti) as required by 251.3(e)(8).

2. Consistent with 21 CFR 201.10(g)(2) and 251.13(b)(1), the established name must be at least half as large as the proprietary name. However, the established name on some of your imported carton or container labeling is less than half as large as the proprietary name (e.g., Dovato, Odefsey, and Rexulti).

3. Consistent with 251.13(b)(4)(i), the Importer's NDC must replace any other NDC otherwise appearing on the label of the FDA-approved drug at the time of importation. However, the NDC on the HOW SUPPLIED/STORAGE AND HANDLING section of the proposed Juluca Prescribing Information (PI) does not match the NDC on the proposed container label.

4. Consistent with 251.13(b)(4)(iii), the name and place of business of the Importer must be included in all imported drug labeling. Human prescription drug labeling includes the PI, patient labeling (Medication Guides (MGs), Patient Package Inserts (PPIs), and/or Instructions for Use (IFUs)), and/or carton and container labeling. However, the name and place of business of the Importer were not included in the proposed patient labeling (MGs, PPIs, and/or IFUs) for all drugs.

5. Consistent with 251.13(b)(4)(iv), the name of the applicant must be included in the following required statement in the HOW SUPPLIED/STORAGE AND HANDLING section (or the HOW SUPPLIED section): [This drug was/These drugs were] imported from Canada without the authorization of [Name of Applicant] under the [Name of SIP Sponsor] Section 804 Importation Program." However, there were several HOW SUPPLIED/STORAGE AND HANDLING sections in the PI's for your proposed imported drugs that did not include the

correct applicant in this required statement (e.g., Dovato, Eliquis, Entresto, Genvoya, Juluca, Odefsey, Prezcobix, Ravicti, Symtuza, and Vraylar).

6. Consistent with 251.13(c), the relabeling and associated limited repackaging activities must meet applicable requirements, including applicable current good manufacturing practice requirements. Except for repackaging that is necessary to perform the relabeling described in the Part 251, further repackaging of drugs imported pursuant to a SIP is prohibited. Repackaging the container closure of a drug is not permitted under Part 251. Accordingly, all strengths of Entresto (sacubitril and valsartan) tablets and Eucrisa (crisaborole) ointment, and the 5 mg strength of Eliquis (apixaban) tablets, are not eligible for importation under Section 804 because, based on the information available, relabeling these drug products would require breaching their container closure systems (e.g., opening the blister pack, tube, or bottle).

7. The SIP proposal does not indicate that the secured warehouse or other secure distribution facility is within 30 miles of the authorized Port of Entry for examination as required by 251.17(b). Currently, the SIP proposal states that the Importer will store and maintain the shipment in the Whitestown, Indiana facility. At this time, the only authorized Port of Entry is Detroit, Michigan. The Whitestown facility is not within 30 miles of Detroit.

8. The SIP proposal indicates that FDA will be notified of certain illegitimate products within 3 business days. This is inconsistent with the DSCSA requirement at section 582(c)(4)(B) of the FD&C Act, which requires that FDA and all immediate trading partners be notified of illegitimate product in the possession or control of the wholesale distributor within 24 hours of such determination. The rule, at 251.14(d)(6), requires that an Importer comply with all applicable requirements of section 582.

Additional Note

We note that while the SIP proposal does not include a detailed description of the Statutory Testing that 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 that 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 21 CFR 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 21 CFR 251.5(c)(4)(xi)(C). This description must be sufficiently detailed for FDA to ensure that the testing will meet the requirements of 21 CFR 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.

We also note that the SIP proposal states that testing will conform to United States Pharmacopeia (USP) where a monograph exists and that, if there is no USP monograph, you will use "testing methods provided by the manufacturer . . . or develop alternative testing techniques that provide consistent, linear results and are developed in accordance with CGMP and International Council of Harmonisation guidelines." None of the drugs listed in the SIP proposal is subject to a USP monograph, so testing methods provided by the manufacturer will be needed to meet the requirements of 21 CFR 251.16(d). Under 21 CFR 251.16(b),

> [u]nless the manufacturer conducts the Statutory Testing, in accordance with this part, the manufacturer of the drugs imported under an authorized SIP must supply to the Importer, within 30 calendar days of receiving the Importer's request, all information needed to conduct the Statutory Testing, including any testing protocols, Certificate of Analysis, and samples of analytical reference standards that the manufacturer has developed. The manufacturer must also provide the Importer, within 30 calendar days of receiving the Importer's request, with formulation information about the HPFB-approved drug, a stability-indicating assay, and the FDA-approved drug to facilitate authentication.

Conclusion

As noted above, FDA is requesting that you provide additional or clarifying information by **28 August 2023**. FDA has identified the above deficiencies with Florida's current SIP proposal. Accordingly, these items will need to be adequately addressed for the SIP proposal to be authorizable. This additional information will assist FDA in making a prompt decision on the SIP proposal.

Please indicate if you intend to provide the additional required information. 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: 2023.08.14 17:18:29 -04'00'

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