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Dockets Management Staff (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**Re: Notice of Proposed Rulemaking, Importation of Prescription Drugs,
Docket No. FDA-2019-N-5711, 84 Fed. Reg. 70,796 (December 23, 2019)**

Dear Reviewers:

The National Academy for State Health Policy (NASHP) is a nonpartisan forum of state policymakers. We explore, lead, and implement innovative solutions to health policy challenges. Working with states, and through our Center for State Prescription Drug Pricing, NASHP developed model policy for allowing states to sponsor, implement, and oversee programs that would allow their populations access to safe and effective prescription drugs at lower cost from Canada. We have worked closely with the states that have enacted laws and are now planning their implementation.

NASHP appreciates this opportunity to comment on the proposed rule for Importation of Prescription Drugs,¹ and commends the President and his Administration, the U.S. Department of Health and Human Services (HHS), and the U.S. Food and Drug Administration (FDA) for taking this important step toward reducing the cost of prescription drugs for American consumers while imposing no additional risk to the public's health and safety.

These comments were developed in consultation with the regulatory and legal advisors at FDAImports.com and Benjamin L. England & Associates and in discussions with state officials. Fully realizing the promise of these proposed rules will require certain revisions detailed below, and an active role for the federal government, partnering with states, to facilitate negotiations with Canada.

¹ FDA, HHS, Importation of Prescription Drugs, 84 Fed Reg. 70796 (December 23, 2019)

I. Background

The last few decades have seen the prices of prescription drugs in the U.S. skyrocket relative to the costs of those same drugs in other developed countries. As FDA acknowledged in the Notice of Proposed Rulemaking (NPRM) for the Importation of Prescription Drugs, brand name drugs (as opposed to generic drugs) cost approximately an average of three times as much in the United States than they do in Canada, and millions of Americans have sought to purchase their physician-prescribed drugs from other countries because they are unable to afford the costs of those same drugs as sold in the U.S.² These mail order strategies, however, may lack oversight and consumer protections, which is why states have sought to develop and oversee prescription drug importation programs that build on current FDA policy and practice to ensure safety.

Absent other federal action to substantially reduce the excessive costs of prescription drugs in the U.S., regulated importation of prescription drugs from Canada is compelling. The authorizing statute for this proposed regulation, section 804 of the U.S. Federal Food, Drug, and Cosmetic Act (FDCA), was passed by Congress and signed by the President in 2003.³ Section 804 of the FDCA, among other things, authorizes the Secretary of HHS to issue regulations permitting pharmacists and wholesalers to import certain prescription drugs from Canada under certain conditions. For section 804 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 will “result in a significant reduction in the cost of covered products to the American consumer.”⁴

II. Our Concerns with the Proposed Rule, Generally

HHS and FDA clearly intend to afford States the opportunity to establish Section 804 Importation Programs (SIPs) under FDCA section 804. This is explicit in the preamble and the body of the proposed rule, as well as in all public statements made by the Department and Agency. HHS and FDA are responding, among other things, to pressure from states that have already enacted legislation to establish a drug importation program under FDCA section 804, which would enable FDA-approved drugs to be purchased from Canada and safely imported for use within their respective state jurisdictions, to significantly reduce the cost of such drugs to their constituents. States have invested substantial time and resources into developing their proposals for submission to HHS and FDA. In fact, in several cases, state legislation was drafted

² 84 Fed. Reg. at 70799-70800 (citing Patented Medicine Prices Review Board (PMPRB), 2017, “Annual Report 2017: Regulating Prices of Patented Medicines: Continued Vigilance Necessary, Bilateral Price Comparisons, Average Foreign-to-Canadian Price Ratios, Bilateral Comparisons”; PMPRB, 2018, “About Us: Mandate and Jurisdiction”; Rachel Bluth, 2016, “Faced with Unaffordable Drug Prices, Tens of Millions Buy Medicine Outside U.S.”; and Kaiser Health News and Kaiser Family Foundation, 2016, “Kaiser Health Tracking Poll—November 2016”).

³ Section 1121 of the Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA, Pub. L. 108-173)

⁴ FDCA section 804(l)(1)

and enacted with a view toward ensuring as much overlap as possible with the existing federal regulatory regime governing safe drug manufacturing, importation, and distribution within an already global market.

FDA, and others,⁵ have often referred to the drug distribution system in the U.S. as being a “closed” system. Calling it a closed system is a misnomer, however, if it is intended to imply the premise that “we do not import prescription drugs into the U.S.” The FDA estimates that, as of 2018, 88% of facilities making active pharmaceutical ingredients (APIs) and 63% of facilities making finished drugs sold in the U.S. are located overseas.⁶ Drug importation is an inherent and necessary part of the U.S. drug distribution system and has been for many years.

States are conscious of the two-prong certification the HHS Secretary must make to Congress: that section 804 drug importation programs will pose no additional risk to U.S. public health and safety and will result in significant cost savings to U.S. consumers. Many states are already substantially down the road of developing their programs, and their draft proposals have been designed to achieve certifiable SIPs. Yet the rule, as proposed, works against what many States are already planning under their respective implementing statutes and what the states have determined to be necessary for a SIP to safeguard consumers and assure consumer savings to achieve the required certification with respect to both risk and savings.

Based upon our review of the NPRM, we are concerned that HHS and FDA have unnecessarily narrowed the scope of section 804 and restricted the process (e.g., in terms of where certain activities must occur and who may engage in them). As a result, many states will be unable to implement their respective programs under the proposed rule. We believe the narrower scope and greater restrictions are unnecessary to ensure drugs imported under a SIP pose no greater health or safety risks than the existing regulatory programs. Furthermore, the narrower scope and greater restrictions would impose unnecessary costs to the federal government, the states, and SIP participants by creating a separate regulatory regime for FDA to manage. In addition to not adding to the safety of drugs imported under a SIP, the restricted processes proposed by HHS and FDA will undermine the federal and state agencies’ abilities to achieve and demonstrate significant cost savings to the consumer. We offer our comments to propose corrections to these problems and to give meaning to Congress’ intent to establish an importation program under section 804.

States have gone to great lengths to evaluate existing federal regulatory requirements that govern approval, sourcing, repacking, relabeling, importation, and distribution of prescription drugs. They have intentionally sought to develop their proposals in accordance with such

⁵ See, e.g., “The Dangers of Drug Importation Pocket Card,” PhRMA, March 14, 2017 (stating, in pertinent part, “The U.S. Food and Drug Administration (FDA) … is focused on protecting our closed drug supply distribution system. Medicines that enter the United States through importation will not be subject to these same strong standards”).

⁶ Congressional Research Service, In Focus: Prescription Drug Importation (Updated November 21, 2019).

existing requirements. States have carefully considered how federal and state authorities could be assured that drugs imported under a section 804 program would be FDA-approved drugs, properly labeled and not adulterated, as required by the FDCA. In so doing, the states have assumed HHS and FDA believe that the existing regulatory framework governing the manufacture, packing, labeling, repacking and relabeling, importation and distribution of prescription drugs from, in, and through existing international supply chains is adequate to assure the safety and efficacy of the millions of prescription drugs imported into the U.S. already. The state proposals have merely adopted, and where necessary, proposed to extend, the FDA's existing regulatory requirements to FDA-approved drugs that were labeled for and purchased in a foreign market, and to bring those drugs to the states' populations through Canadian distributors and repackagers/relabelers that are registered with FDA, regulated by FDA and Health Canada, and reviewed and audited by the state.

Given that current FDA law and regulations already ensure the safety of drugs sold within the U.S., and the majority of those drugs are manufactured overseas, we believe many of the proposed rule's additional restrictions go too far. In our opinion, FDA's existing drug approval process (including its inspection and approval of finished drug manufacturers) provides the fundamental basis for ensuring that an FDA-approved prescription drug made by the FDA-approved prescription drug manufacturer for distribution in another country is safe and effective for its FDA-approved uses *provided that* the FDA-approved drug is authentic, its final labeling is FDA-approved, and the drug has not degraded while in the international supply chain. Any other conclusion runs against the current reality of drug manufacturing and distribution in international markets that supplies the current U.S. drug market. Drugs made wholly or in-part overseas move through the international supply chain using the services of third-party logistics providers, international carriers, freight forwarders, customs brokers, agents, repackagers and relabelers, etc. Drug companies do not own or operate the international supply chains that import the vast majority of finished drugs and APIs dispensed in the U.S. Many active pharmaceutical ingredients are manufactured by contract third parties - not by New Drug Application (NDA) (or Abbreviated New Drug Application (ANDA)) sponsors or holders. Many, if not the majority of, finish-packed prescription drugs are packaged and labeled by contracted third parties, whether in the U.S. or abroad.

Section 804 contemplates importers or pharmacists (here we restrict our analysis to States) will obtain for importation into the U.S. an FDA-approved drug in the international supply chain, ensure that its labeling conforms to the FDA-approved NDA or ANDA, and test the drug to confirm it is authentic and to ensure it is not degraded. Implementation of section 804 of the FDCA should not be complicated given the fact that FDA already regulates all of these activities and given the current international scope of drug manufacturing, packing, labeling, and distribution. The States are prepared to establish and administer SIPs and provide support to the FDA in overseeing these SIPs. However, to deliver cost savings to U.S.

consumers these programs cannot be weighed down by unnecessary restrictions that add no meaningful safety benefit.

Some of the excessively restrictive provisions that the proposed rule would impose on SIPs include:

- Requiring the indefinite shutdown of the entire SIP if any aspect of the SIP, no matter how small or contained, does not meet any applicable requirement,
- Requiring all sampling, statutory testing, and relabeling of drugs covered by a SIP to occur only during the importation process and within the physical confines of a Foreign Trade Zone or port area, and
- Reserving for the FDA the authority to terminate a SIP after two years for no reason whatsoever.

These, and other such proposed provisions, are not necessary to ensure drugs imported under a SIP impose no additional risk to the U.S. public health and safety. Even in the absence of every restriction in the proposed rule that goes beyond what is explicitly required by section 804, provisions in the FDCA that apply to prescription drugs would apply to prescription drugs imported under a SIP. For example:

- All drug manufacturers, repackagers, relabelers, wholesale distributors, and pharmacists participating in a SIP would have to be duly registered and would be regulated by FDA and subject to FDA inspection,
- All drugs being imported into the U.S. under a SIP would have to meet all the requirements specified by the FDA approval for the drug, including being safe and effective for their intended uses and being properly labeled for the U.S. market,
- All drug manufacturers, repackagers, relabelers, and wholesale distributors participating in a SIP would be subject to the vast majority of the requirements of the Drug Supply Chain Security Act (DSCSA),
- All drug manufacturers, repackagers, relabelers, and wholesale distributors in Canada participating in a SIP would also be regulated by Health Canada and subject to inspection by Health Canada,
- All drugs being imported under a SIP would be subject to testing for authenticity and degradation prior to being imported into the U.S., which, notably, is not a requirement for any drugs imported outside of a SIP, and
- All drug manufacturers, repackagers, relabelers, and wholesale distributors participating in a SIP would have to comply with all additional requirements imposed by the specific SIP, or risk expulsion from the SIP.

The above list is, of course, hardly a comprehensive list of the many requirements that would apply to SIP participants and to drugs imported under a SIP even without the additional restrictions in the proposed rule.

There are a few provisions in the FDCA, all of them added by the DSCSA, that generally could be inapplicable to SIPs. However, the final rule can compensate for the inapplicability of these FDCA/DSCA provisions without imposing excessive restrictions and costs on SIPs that are unnecessary to prevent any additional risk to the U.S. public's health and safety.

As explained by FDA in the NPRM,⁷ FDA would use its authority under section 582(a)(3)(iii) of the FDCA to exempt SIPs from certain DSCSA requirements. More specifically, FDA would exempt SIPs from the DSCSA requirement that the U.S. Importer only accept prescription drugs to which the manufacturer affixed a unique product identifier⁸ and from the DSCSA requirement that the U.S. Importer only accept prescription drugs about which the manufacturer provided certain specific transaction history and certifications.⁹ Practically speaking, these requirements could typically not apply to prescription drugs imported under a SIP because the drug manufacturer is required to comply with these requirements only if the manufacturer intends the drug to be sold in the U.S. These two requirements primarily exist to allow for verification of the identity and transaction history of the drug prior to its importation into the U.S. We support some of the proposed rule's provisions that would reasonably account for these inapplicable DSCSA requirements. For example, we support the proposed provisions that would require that the drug manufacturer sell the prescription drug directly to a Canadian Foreign Seller in a single transaction (see, e.g., proposed § 251.14(d)) and that would require a Canadian Foreign Seller receiving the drug from the manufacturer to apply a unique identifier to the drug (see, e.g., proposed § 251.14(c)(4)(ii)).

FDA would also exempt SIPs from the requirement that U.S. Importers only accept drugs from entities that meet the DSCSA's definition of an authorized trading partner.¹⁰ Foreign Sellers could generally not meet DSCSA's definition of an authorized trading partner because Foreign Sellers would be considered to be wholesale drug distributors, FDA requires wholesale drug distributors to be licensed by a U.S. state,¹¹ and states generally do not license foreign wholesale drug distributors. However, the Foreign Seller participating in a SIP would have to be duly licensed by Health Canada, be registered as a wholesale drug distributor with FDA (pursuant to section 804(f) of the FDCA), and FDA would have to approve of the foreign seller's participation in the SIP based on a comprehensive review of its compliance history (see, e.g.,

⁷ See 84 Fed. Reg. at 70816.

⁸ See sections 582(c)(2), (d)(2), (c)(4)(A)(i)(II), and (d)(4)(A)(ii)(I)(II) of the FDCA.

⁹ See sections 582(c)(1)(A) and (d)(1)(A) of FDCA.

¹⁰ See 84 Fed. Reg. at 70816, citing the requirement of FDCA section 582(c)(3) and (d)(3).

¹¹ Although section 583 of the FDA grants FDA the authority to establish a federal licensing system for wholesale drug distributors, FDA has not done so.

proposed § 251.3(d)). Accordingly, there would be no additional risk to the U.S. public health and safety if the Foreign Seller is not licensed by a U.S. state.

As we note above, there are certain provisions in the proposed rule that would reasonably account for the inapplicability of these FDCA/DSCSA requirements. However, as we discuss below, many provisions of the proposed rule are unnecessary with respect to ensuring that SIPs do not pose any additional risk to the U.S. public's health and safety and these provisions should be modified or eliminated.

In our opinion, many of the proposed rule's provisions significantly diminish the likelihood that any SIP implemented under this rule will successfully satisfy the two prongs of safety and cost savings. The various programs the states have designed and will propose extend the documentation requirements of the Drug Supply Chain Security Act (DSCSA) into the foreign supply chain, incorporate the testing requirements of FDCA Section 804, and include audit components. As a result, drugs imported under the states' proposed programs would be subject to greater regulatory and safety oversight than the millions of prescription drugs imported every day by drug companies under FDA's current regulatory importation program.

Moreover, the proposed rule would create various openings for drug companies to circumvent and undermine SIPs, would provide insufficient incentives for Canada to support the program, and would restrict potential economies of scale.

An overview of our comments is set out below, followed by our full comments. We urge the FDA to make the necessary revisions to the proposed rule to ensure that the rule achieves significant reduction in the cost of prescription drugs to Americans while posing no additional risk to Americans' health and safety. We look forward to continued engagement with the Administration, HHS, and FDA on this rule.

III. Overview of our comments:

- A. State agency SIP Sponsors should not be limited to the state agency that regulates wholesale drug distribution and/or the practice of pharmacy in the state. Such a limitation would conflict with many state legislative mandates for SIPs and would be otherwise impractical.**
- B. The final rule should allow FDA to conditionally approve SIPs that do not initially specify the Importer(s), Foreign Seller(s), relabeler(s), and repackager(s). The rule should allow FDA to later fully approve the SIP when that information is provided. Potential SIP participants are unlikely to sign-on to participate in a SIP framework that has not been approved. The federal government should partner with the states in facilitating these arrangements, as appropriate.**

- C. As written, the proposed rule would prohibit FDA approval of initial SIP Proposals that include multiple Foreign Sellers in Canada, both horizontally and vertically. Doing so will allow for more robust and effective SIPs. Not doing so, on the other hand, would allow drug manufacturers to discriminate against the one or few Foreign Seller(s) specified in SIPs, preventing SIPs from demonstrating to FDA that they can consistently and successfully import prescription drugs. The SIP would, essentially, be over before it began.
- D. Prohibiting the relabeling (and repackaging activities necessary to perform the relabeling) from being conducted in Canada adds unnecessary cost to SIPs without preventing additional risk and misses a clear opportunity to engender Canadian support for SIPs. Moreover, requiring all relabeling activities to occur within close proximity of the port, or within the confines of a Foreign Trade Zone, is an unreasonable restriction.
- E. FDA should allow statutory testing in the U.S. to be conducted after the drug is relabeled in Canada, or alternatively, FDA should allow the sampling, for statutory testing in the U.S., to be conducted in Canada. This would allow relabeling of covered drugs to be conducted by qualified Canadian relabeling operations, which would in turn engender Canadian support for the program and lower relabeling costs for SIPs, without undermining quality or imposing additional risks to the public's health and safety.
- F. A blanket prohibition against allowing a SIP to propose, and for FDA to consider, the importation and repackaging of specified bulk eligible prescription drugs under a SIP will eliminate opportunities to deliver additional savings to U.S. consumers at no additional risk.
- G. If FDA is to require laboratories that conduct statutory testing under a SIP to have an FDA inspection history, FDA should first demonstrate that a significant number of such laboratories exist throughout the U.S. FDA typically does not inspect independent drug testing laboratories.
- H. SIP sponsors should be allowed to tailor their corrective actions to the problem. Requiring the SIP Sponsor to suspend the entire SIP if they determine any aspect of the SIP does not meet an applicable requirement of the FDCA, FDA regulations, or SIP is unduly burdensome and overbroad. Unless the problem affects consumer safety or program integrity, corrective action should be allowed to remedy identified concerns.
- I. Categorically excluding drugs subject to a Risk Evaluation and Mitigation Strategies (REMS) from being eligible for importation under a SIP ignores the fact

that REMS vary widely in their requirements. Many REMS could be implemented effectively under a SIP with no additional risk, thereby providing U.S. consumers with a lower cost drug that FDA would have otherwise categorically prohibited from importation under a SIP.

- J. Allowing SIPs to automatically terminate after two years if not proactively extended by FDA would set SIPs up to fail by discouraging investment and participation in the SIP.
- K. The final rule should rely as little as possible on requiring manufacturers to take certain actions and make certain disclosures. Manufacturers are likely to fight these requirements and delay as much as possible. The rule should primarily rely on other measures where possible to achieve the same aims. FDA must also be prepared to provide any necessary information that a manufacturer refuses to provide and to take any other action against the manufacturer as appropriate.
- L. The final rule should not include duplicative Adverse Event and ICSR Reporting Requirements and Recall Requirements. Further, it would be inappropriate to establish a novel “medication error” reporting requirement only for SIPs. This important issue should be addressed throughout the market and not limited to SIPs.
- M. The severability provision is too broad, and risks the entire rule being thrown out on a technicality. It should be tailored to specifically address FDA’s underlying concerns.
- N. Comments on how to estimate savings under a SIP
- O. Comments on timelines for FDA’s review of SIP proposals

IV. Comments in Full:

- A. State agency SIP Sponsors should not be limited to the state agency that regulates wholesale drug distribution and/or the practice of pharmacy in the state. Such a limitation would conflict with many state legislative mandates for SIPs and would be otherwise impractical.

If a state wishes to implement a SIP for its population, the proposed rule would require (under both Option 1 and Option 2) that the SIP Sponsor be “a State … entity that regulates wholesale drug distribution and/or the practice of pharmacy” (see the definition of “SIP Sponsor” in proposed § 251.2). In most states, regulating wholesalers and pharmacies is the responsibility of the state Board of Pharmacy (BoP). However, to date, no state law has designated its BoP to be responsible for designing or implementing the state’s SIP, because in these states BoPs generally do not have the staffing or resource capacity to operate a SIP. State BoPs are often quasi-governmental or housed in a state regulatory agency with broad oversight responsibilities over many industries, and their board members balance their BoP responsibilities with their full-time jobs as health professionals.

States need flexibility to administer their SIP with state agencies that have the capacity to meet the demands of designing and implementing a robust program that can assure safety of the drugs imported and deliver savings to consumers. State laws have identified the following lead agencies as responsible to design, and in most cases, implement their SIP: Agency for Human Services (Vermont), Department of Health Care Policy and Financing (Colorado), Agency for Health Care Administration (Florida), and the Department of Health and Human Services (Maine). Lead agencies have – and should – work in consultation with their state BoP to design and implement their SIPs. However, requiring that the BoP actually *be* the SIP sponsor is too restrictive, in many cases unrealistic, and contradicts the reasoned judgement of these state governments.

The FDA should therefore consider altering the definition of SIP sponsor in the final rule as follows: “*a State, tribal, or territorial governmental entity that has been duly authorized by the State, tribe, or territory (as applicable) to administer a SIP, and which includes in its application a certification that it has the necessary capacity to administer a SIP and that it will collaborate with the State, tribal, or territorial governmental entity or entities that regulate wholesale drug distribution and the practice of pharmacy.*”

B. The final rule should allow FDA to conditionally approve SIPs that do not initially specify Importer(s), Foreign Seller(s), relabeler(s), and repackager(s). The rule should allow FDA to later fully approve the SIP when that information is provided. Potential SIP participants are unlikely to sign-on to participate in a SIP framework that has not been approved. The federal government should partner with the states to facilitate these arrangements, as appropriate.

Under the proposed rule, FDA would not look at an otherwise complete SIP proposal unless the SIP proposal specifies, and provides certain information about, the Foreign Sellers(s), Importer(s), relabeler(s), and repacker(s) that would participate in the SIP.

However, based on our experiences speaking with various potential SIP participants about FDA’s implementation of section 804, most potential SIP participants (i.e., Importer(s), Foreign Seller(s), relabeler(s), and repacker(s)) are hesitant to sign onto a SIP, and undertake the associated obligations (e.g., agreeing to the necessary contractual obligations and registering with FDA as a Foreign Seller), if the SIP has not yet been approved (at least conditionally) by FDA. It is a chicken-or-the-egg dilemma.

This would also set up an impossible standard for SIP proposals to meet and would set pre-SIP negotiations up for failure. Presumably, potential SIP participants must meet certain minimum standards, but HHS and FDA have not yet articulated those standards. Additionally, it may not be clear how many Canadian foreign sellers FDA would approve for participation in any particular SIP (we address this further in the next section). Yet HHS and FDA are requiring the states to vet multiple contract bidders for various supply chain roles for a SIP that has not yet been approved. This restriction unnecessarily stifles participation by market actors that are critical to creating sufficient economies of scale (and competition) to help keep prices for drugs safely imported through the program low enough to provide significant savings to consumers.

Accordingly, we recommend FDA revise proposed 21 CFR § 251.3 to allow a SIP Sponsor to submit, and for FDA to conditionally approve, a SIP proposal that does not specify, nor provide information about, the Foreign Sellers(s), Importer(s), and relabelers and (if any) repackagers that will participate. In other words, FDA could grant conditional approval to a SIP proposal that does not contain the information described by proposed 21 CFR §§ 251.3(c)(6), (7), and (8); (d)(2), (3), and (4); and certain information in (d)(1). The SIP Sponsor would then identify and enroll the Foreign Sellers(s) and Importer(s) and submit the remaining necessary information to FDA.

This proposed revision would have no negative effect on safety of the drugs eventually imported under the program, and it would enhance the SIP Sponsor’s ability to construct and enforce conditions in the initial contracts with the Foreign Sellers and Importers. The revision would also enable the SIP Sponsors to more thoroughly vet necessary prospective commercial participants across applicants to advance both certification prongs in section 804.

We would further encourage the engagement of the Federal government in partnering with states to facilitate these negotiations and discussions with appropriate Canadian officials.

C. As written, the proposed rule would prohibit FDA approval of initial SIP Proposals that include multiple Foreign Sellers in Canada, both horizontally and vertically. Doing so will allow for more robust and effective SIPs. Not doing so, on the other hand, would allow drug manufacturers to discriminate against the one or few Foreign Seller(s) specified in

SIPs, preventing SIPs from demonstrating to FDA that they can consistently and successfully import prescription drugs. The SIP would, essentially, be over before it began.

As proposed, the rule would require that a SIP can initially only designate a single Foreign Seller and a single U.S. Importer (21 CFR § 251.3(a)). The proposed rule would allow the SIP Sponsor to propose additional Foreign Sellers and Importers only *after* the SIP has met the threshold of demonstrating that it has “consistently imported eligible prescription drugs” under the rule for an unspecified period (21 CFR § 251.8(b)). Under this approach, a single specified Foreign Seller would be expected to purchase all covered prescription drugs directly from manufacturers and directly export those prescription drugs to the Importer in the U.S.

A manufacturer of a drug that it sells at a much higher markup in the U.S. is unlikely to sell its product at a lower price directly to a Foreign Seller who they expect will export the drug to the U.S. under a SIP. Accordingly, a SIP with one Foreign Seller is unrealistic. It would be much more reasonable to expect that a SIP would, at minimum, specify multiple established Foreign Sellers in Canada who purchase covered drugs directly from the manufacturers for importation under the SIP, and either export those drugs to the U.S. directly or specify a second Foreign Seller in Canada who would purchase the covered prescription drugs from those Foreign Sellers to consolidate for exportation. As proposed, 21 CFR § 251.3(a) is self-defeating because it is unlikely that any SIP with only a single Foreign Seller would ever be able to consistently import eligible prescription drugs from Canada under the rule.

FDA did note in the NPRM, however, that it is open to issuing the final rule so that it would allow for a SIP, from the start, to have multiple Foreign Sellers. We urge FDA to allow multiple Foreign Sellers in a SIP in the final rule. Further, FDA has proposed associated potential revisions of 21 CFR §§ 251.14(a)(4), 251.19(c), and 251.19(d)(2), described at 84 Fed. Reg. 70814 (December 23, 2019), that would implement this option and institute certain additional safeguards to account for the longer supply chains. We support the final rule allowing for a SIP to have multiple Foreign Sellers, and we support the alternative provisions of 21 CFR §§ 251.14(a)(4), 251.19(c), and 251.19(d)(2), described at 84 Fed. Reg. 70814 (December 23, 2019).

We also support FDA’s alternative proposed 21 CFR § 251.3 (as described at 84 Fed. Reg. 70814), which would allow multiple Foreign Sellers in an initial SIP, although we request that FDA further revise it such that it states, in pertinent part, that a SIP could include “additional” Foreign Sellers rather than “subsequent” Foreign Sellers. A SIP Sponsor should have the opportunity to demonstrate that including additional Foreign Sellers both vertically (i.e., multiple (“subsequent”) Foreign Sellers in a single supply chain) and additional Foreign Sellers horizontally (e.g., multiple Foreign Sellers who purchase drugs directly from the manufacturer) would result in a significant reduction in the cost of covered products to the American consumer and pose no additional risk to the public’s health and safety. For example, the SIP Sponsor could demonstrate why existing regulatory safeguards are sufficient or, if the SIP proposal is

particularly complex, how additional requirements specific to a Sponsor's SIP would address any potential risks.

Allowing for this flexibility in the specified supply chains under a SIP will also help account for the wide variety of supply chains that currently exist for drugs. For example, a potential Foreign Seller might only import and distribute specific prescription drugs, a manufacturer of an eligible prescription might sell only to one or two specific potential Foreign Sellers in Canada, or a potential Foreign Seller that only imports and distributes eligible prescription drugs might not be interested in also becoming an exporter. Further, as we noted above, allowing for multiple specified Foreign Sellers across the Canadian market, for a single specified covered drug, will help prevent large manufacturers from using their market power to undermine a SIP by, for example, refusing to sell drugs to the Foreign Seller specified in a SIP.

This approach, in and of itself, poses no inherent additional risk to the public's health and safety. First, in accordance with FDA's proposal, the Foreign Seller who is the importer of the drug to Canada must import the drug directly from the manufacturer of the drug, and the drug would thereafter feature a unique product identifier. The requirement for this single direct transaction between the manufacturer and the Foreign Seller ensures that there is no additional risk posed by the drug, even though the transaction would be excepted from the DSCA product identifier requirement and the DSCA requirement for transaction documentation beyond the transaction documentation required by Canadian law. Furthermore, FDA would be able to deny any proposed SIP that does not sufficiently demonstrate that including additional specified Foreign Sellers in the SIP would pose no additional risk to the public's health and safety. In our opinion, however, no particular additional safeguards would be necessary to include in the rule under this approach, particularly if the SIP is only proposing to add a single Canadian Foreign Seller to one or more supply chains.

Under the proposed requirement that a Foreign Seller purchase the drug directly from the manufacturer, and under the provisions of the proposed rule that directly implement requirements of section 804, the transaction between the Foreign Seller who purchased the drug directly from the manufacturer, and the transaction between all subsequent Foreign Sellers who purchase the drug, and the transaction between the final Foreign Seller (the Canadian exporter) and the U.S. Importer, would be fully documented –especially if the proposed revisions to 21 CFR §§ 251.3, 251.14(a)(4), 251.19(c), and 251.19(d)(2), as described at 84 Fed. Reg. 70814, are included in the final rule.

Furthermore, every Canadian drug supply chain participant is highly regulated by Health Canada. Even the Canadian importer of the drug must hold an Establishment License from Health Canada; must be a registered medical practitioner, drug manufacturer, drug wholesaler, or pharmacist; and is only able to import drugs manufactured at the manufacturing sites listed on their Establishment License (see, e.g. Guidance Document on the Import Requirements for

Health Products under the Food and Drugs Act and its Regulations (GUI-0084), Health Canada, June 1, 2010).

We note that under this approach minor additional changes would also need to be made to certain provisions of the proposed rule to account for one (or more) subsequent foreign sellers under a SIP. For example, proposed § 251.14(c)(4)(i) would need to be revised to “Separate the portion of drugs *ultimately* intended for sale to the Importer located in the United States...” and proposed § 251.14(c)(1)(i) would need to be revised to “...that it intends to sell to the Importer or *subsequent Foreign Seller* under a SIP is a suspect foreign product....” or similar.

FDA should also allow a SIP to propose more than one Importer in the U.S., if justified by the SIP proposal. Such an allowance would not impose any additional risk, as the Importers would be located in the U.S. and be directly overseen by both FDA and the state. A SIP Sponsor may want to use more than one U.S. Importer under the SIP for a variety of reasons, such as encouraging price competition between the two Importers.

FDA should also permit different SIPs to share Foreign Sellers and Importers. This simple revision would enable States to share in the regulatory burdens, audits, and testing required under their respective SIPs, thereby reducing costs and fees associated with the operation and regulation of the programs. This revision will also increase the likelihood that the SIP Sponsors will detect any suspect or illegitimate drugs and detect any violations by shared Foreign Sellers or Importers.

D. Prohibiting the relabeling (and repackaging activities necessary to perform the relabeling) from being conducted in Canada adds unnecessary cost to SIPs without preventing additional risk and misses a clear opportunity to engender Canadian support for SIPs. Moreover, requiring all relabeling activities to occur within close proximity of the port, or within the confines of a Foreign Trade Zone, is an unreasonable restriction.

There is no compelling justification for why the relabeling of the drug must occur during the importation process instead of in Canada prior to importation. FDA’s prohibition will significantly increase costs in the supply chain as well as the costs of FDA’s own administrative activities in managing the program, with no effect on health and safety risks relative to current practices. Accordingly, the proposed rule should allow relabeling (and any limited repackaging required to relabel the drug) to be conducted in Canada by a Foreign Seller or Importer (or under contract with the Foreign Seller or Importer). In any case, the entity physically conducting the relabeling (and any limited repackaging) would have to be registered as a repackager or relabeler with FDA (as is already required under FDA regulations) and would be subject to all FDCA requirements for repackagers and relabelers (e.g., DSCSA obligations and allowing FDA inspections). Further, allowing relabeling to occur in Canada would engender Canadian support

for the overall Section 804 program by providing economic opportunities for Canadian relabelers and repackagers.

Moreover, in addition to being subject to all applicable FDCA and DSCSA requirements, the repackager or relabeler in Canada would be, as they are today, registered with and regulated by Health Canada. Repackagers and relabelers in Canada are highly regulated entities, just like in the U.S. Under the Canadian Food and Drug Regulations, Part C Divisions 1A and 2, any person who fabricates, packages, labels, tests, imports, or distributes drugs, or wholesales certain drugs, in Canada, must have and maintain a Drug Establishment License, must follow specific Good Manufacturing Practices (GMPs), and are subject to inspection by Health Canada, among other requirements (in addition to their obligations under the FDCA and DSCSA).

It is noteworthy that FDA has formally expressed confidence in Canada's drug establishment inspections. Since 1973 FDA and Health Canada have operated under an Agreement of Cooperation relating to inspections.¹² Under that agreement, FDA and Health Canada, among other things, coordinate their inspection of drug establishments in each other's countries and have committed to promptly exchange inspection reports upon request. So, without some compelling justification, FDA should rely on the existing regulatory framework governing drug relabeling (and repacking) that already exists, rather than force a new framework that exists only in a U.S. Foreign Trade Zone (FTZ) or the in the immediate area of a U.S. port.

The proposed rule could even require the U.S. Importer to take title to the drugs in Canada prior to relabeling, to place the regulatory obligation on a U.S. entity (the Importer) to contract with a repackager or relabeler in Canada and ensure labeling (and any limited repackaging) is conducted properly.

The proposed rule also appears to require that the relabeling of all drugs imported under a SIP be conducted at a secure warehouse within 30 miles of the authorized port (or, presumably, within the physical confines of the FTZ) (see proposed § 251.17(b), requiring that the covered drugs remain at a secured warehouse from the time they arrive in the U.S. until FDA issues an admissibility decision). This is highly impractical, would be extremely expensive, would upset warehouse storage availability and rates along the border near the ports used for SIPs, and would seriously complicate FDA's own administrative implementation of the program. This proposed provision only exists because FDA contemplates detaining the shipment imported under a SIP as unapproved and misbranded and then supervising the testing and relabeling as a condition of release. Requiring the sampling, testing, and relabeling of the drug to be conducted with the physical confines of an FTZ presents similar problems. These restrictions are unnecessary at

¹² Available here: <https://www.fda.gov/international-programs/cooperative-arrangements/fda-canadian-department-national-health-and-welfare-agreement-cooperation>

best and extremely ill-advised at worst, as they add no benefit to the safety of drugs imported under a SIP.

FDA provides no justification for requiring relabeling to occur within 30 miles of the authorized port of entry and no statistics indicating there are any FDA-registered repackers/relabelers operating secured warehouses in such areas. Further, even if an FDA-registered relabeling facility were considered to qualify as a secured warehouse under the rule, requiring the relabeling to occur at a drug relabeling facility within 30-miles of the authorized port or within an FTZ may be impossible, or, in a port area or FTZ with only one or few FDA-registered drug relabelers, would likely result in the relabeler(s) charging monopoly prices.

As we note above, FDA already regulates prescription drug relabelers (and repackers), as does Health Canada. Much of the drugs imported by drug companies are in bulk, lacking finished packaging and labeling. Drug repacking and relabeling services are routinely contracted out by drug manufacturers and these operations occur in the U.S. and abroad. FDA's existing regulatory regime already contemplates repacking and relabeling of FDA-approved drugs in foreign jurisdictions by third parties. The recommendation to permit relabeling and repackaging in Canada is consistent with FDA's current regulatory framework, will keep the costs of drugs imported under a SIP low, and allows for evaluation by FDA, by Health Canada, or even by the participating states using accredited third-party inspection services.

E. FDA should allow statutory testing in the U.S. to be conducted after the drug is relabeled in Canada, or alternatively, FDA should allow the sampling, for statutory testing in the U.S., to be conducted in Canada. This would allow relabeling of covered drugs to be conducted by qualified Canadian relabeling operations, which would in turn engender Canadian support for the program and lower relabeling costs for SIPs, without undermining quality or imposing additional risks to the public's health and safety.

The proposed rule would require statutory testing to occur in the U.S. We acknowledge this is effectively required by section 804's definition of a qualifying laboratory as being, in pertinent part, a laboratory in the U.S. However, this does not mean that relabeling (and any necessary limited repackaging) must also occur in the U.S. during importation. As we note above, prohibiting the relabeling and repackaging from being conducted in Canada misses a key opportunity to engender Canadian support for SIPs without imposing additional risk to Americans. Moreover, such a prohibition would add unnecessary expenses to SIPs.

First, relabeling and repackaging could occur in Canada prior to statutory testing. SIP participants would have no incentive to relabel and repackage inauthentic or degraded drugs that will be later subject to statutory testing for authenticity and degradation. FDA states that statutory testing prior to relabeling is necessary to prevent having relabeled drugs that failed

testing being refused entry and exported back to Canada where they may subsequently be sold illegally back into the United States or elsewhere (see 84 Fed. Reg. at 70805). To the extent that may be a risk, despite all the safeguards under the FDCA, DSCSA, section 804, and the proposed rule to prevent importation of drugs with unclear supply chain histories, this concern can be resolved. For example, FDA could require, as condition of approval of a SIP, that if FDA tests and/or detains any drug imported under a SIP, and the drug fails authenticity or degradation testing or is otherwise determined to not meet the requirements of FDCA or SIPs, then the drugs (if they cannot be reconditioned -e.g., via segregation) must be destroyed or be permanently relabeled to show they have failed statutory testing (e.g., by using stickers that will destroy the label if they are removed).

Alternatively, relabeling (and any necessary limited repackaging) could still be required to be conducted in Canada after statutory testing if the sampling for statutory testing is permitted to occur in Canada. Although not explicitly stated in the NPRM, presumably FDA's justification for requiring the sampling to occur during the importation process after arrival of the drug in the U.S. is to ensure that the samples that are tested accurately represent the condition of the drug at the time the drug is offered for import.¹³ We do not agree that FDA's proposed approach is necessary to achieve that end if the sampling were allowed to occur in Canada prior to importation to the U.S. Of note, FDA could allow importation of the samples for testing purposes under section 801(d)(3)(A) of the FDCA, and the samples could be destroyed after statutory testing in accordance with 801(d)(3)(A)(iii).

Unless FDA plans to supervise sampling of all drug lots imported under SIPs for testing under the proposed rule and therefore require the sampling to occur in the U.S. (for convenience), there is no greater risk of mistake (or fraud) in sampling, documentation of the relevant lot, or accuracy of the test result whether the drugs are sampled in Canada or the U.S.

Moreover, FDA would retain the ability under section 801(a) of the FDCA to test any covered drug when the covered drug is offered for import into the U.S., and/or to detain any covered drug offered for import if FDA determines that the drug appears to be degraded (under an adulteration charge), to not meet the requirements of an NDA (under an unapproved drug charge), and/or be inauthentic (under an adulteration and/or misbranding charge, depending on the specifics) or counterfeit. At that time FDA may detain the drug under FDCA section 801(a) and require that the Importer either accept FDA's determination or perform steps to demonstrate to FDA that the drug is not adulterated, unapproved, or misbranded (including counterfeit).

¹³ This was FDA's justification in the NPRM for the proposed Laboratory Accreditation for Analyses of Foods rule for requiring that testing of food under section 801(a) of the FDCA (i.e., testing, conducted by or on behalf of importers, of food FDA has detained at the border on the basis that it appears to be adulterated, misbranded, or violate certain other provisions of the FDCA) be conducted in the U.S. under the supervision of FDA (see 84 Fed. Reg. 59465 (November 4, 2019)). However, even then FDA proposed to allow testing of the food to occur prior to arrival of the food in the U.S. if FDA is able to determine that the tested sample is representative of the food at the time the food is offered for import.

Furthermore, the U.S. Importer and the exporter (the Foreign Seller) of the drug would both remain subject to FDA's jurisdiction and FDA would have received comprehensive information about the drug through the applicable Section 804 pre-import request and the entry information FDA would receive pursuant to proposed 21 CFR § 1.74(b)).

FDA's proposed requirement for sampling and relabeling to all occur after the product physically arrives in the U.S. but before the drug is officially admitted into the U.S. also sets up an importation regime that is more cumbersome, more burdensome, and more expensive for FDA to implement. In that regard it is also ill-advised. Because all drugs imported under every SIP under the rule, as proposed, would be misbranded (due to the Canadian labeling of the drugs) and would not have been tested yet, FDA would be obligated to detain every such shipment (or monitor it in an FTZ) and directly supervise the reconditioning process under a Customs bond (via either a basic importation bond or a custodial bond permitting manipulation in an FTZ) and follow the drug through the testing and relabeling process to final disposition of the shipment. None of this added expense or allocation of FDA resources would be necessary if the proposed rule permitted relabeling prior to statutory testing or permitted sampling in Canada. Failing drugs would never arrive in the U.S. FDA would not have to detain them, track them, supervise their reconditioning, and release or refuse the shipments. Because there would be no need to refuse shipments of drugs that are never imported, FDA and Customs would be relieved of the expense associated with supervising exportation or destruction of the drug (or, if adopted, relabeling in a manner that the drug is marked as failing under a SIP importation).

FDA's proposal significantly increases federal agencies' and states' costs of implementing Section 804 with no added safety benefit.

F. A blanket prohibition against allowing a SIP to propose, and for FDA to consider, the importation and repackaging of specified bulk eligible prescription drugs under a SIP will eliminate opportunities to deliver additional savings to U.S. consumers at no additional risk.

It is not uncommon for prescription drugs to be purchased and imported directly into Canada in bulk from the manufacturer. However, under the proposed rule, a SIP could not provide for a Foreign Seller to purchase an eligible prescription drug in bulk. Rather, the Foreign Seller could only purchase the drug after it has been packaged and labeled for the Canadian market. This restriction creates inefficiencies because these labeled drugs would be more expensive to purchase and would have to be stripped of their original Canadian packaging and/or labeling before being relabeled (with any limited repackaging) for the U.S. market.

In the preamble, FDA provides its reservations against repackaging of covered drugs under a SIP, as follows (see 84 Fed. Reg. at 70819):

- Repackaging that breaches the immediate container closure system introduces unnecessary risk of adulteration, degradation, and fraud,
- If the container closure systems include a tamper-evident seal, the seal would be disturbed if repackaging were allowed
- 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; and additional stability studies would generally be required to establish a new expiration period.

None of these are insurmountable barriers for repackaging conducted under a SIP by reputable and experienced FDCA-compliant repackagers with positive FDA inspection histories (note: repackagers and relabelers in Canada are also subject to inspection by Health Canada and must also comply with stringent good manufacturing practices, in accordance with Canadian Food and Drug Regulations - Part C, Division 2). Further, the testing requirements of section 804 and the proposed rule add additional safeguards for preventing and detecting any degradation. Because repackagers in Canada would be obligated under a SIP to follow GMPs and are fully qualified to repackage bulk drugs, there is no valid basis to be concerned that repackaging in Canada prior to export would be any more likely to introduce adulterants or to degrade the drug than if the bulk tablets were imported by the drug manufacturer and repackaged in the U.S. Further, various additional precautions could be taken to protect against any fraud risks, and additional stability studies could be conducted if necessary.

Many drugs imported today by drug manufacturers are imported in bulk and subjected to repackaging and labeling by a contracted third-party. Many of the drugs imported today in finished packaging were repackaged and relabeled by third party contract operators abroad. There is no reason to believe that repackaging (and relabeling) in Canada of bulk tablets of a covered drug, after testing, would introduce risk of adulteration or degradation that would not similarly be present when drug manufacturers act as the importer of record. FDA's regulatory framework is designed to manage bulk drug repackaging and labeling and does so adequately. We recommend applying the existing framework rather than attempting to create a new and different drug importation regulatory system.

Accordingly, FDA should permit repackaging and relabeling of bulk tablets in Canada by FDA-registered and Health Canada licensed repackagers and relabelers after testing has been performed. At a minimum, the rule should allow FDA to consider on a case-by-case basis whether to approve the importation of drugs repackaged in Canada from bulk and relabeled in Canada under a SIP. If FDA still has concerns under this approach, the final rule could include additional testing and relabeling provisions that apply to specific bulk prescription drugs imported under a SIP.

G. If FDA is to require laboratories that conduct statutory testing under a SIP to have an FDA inspection history, FDA should first demonstrate that a significant number of such laboratories exist throughout the U.S. FDA typically does not inspect independent drug testing laboratories.

Because of the wide variety of tests that will likely need to be validated and conducted under SIPs to fulfill statutory testing requirements under section 804, it will be important that a wide range of laboratories are eligible to conduct the statutory testing. The proposal at 21 CFR § 251.15(b) to require laboratories that conduct statutory testing under a SIP to have an FDA inspection history could severely limit the number of eligible laboratories. That in turn could significantly increase costs and cause delays for drugs being imported under a SIP.

Presumably, statutory testing under the rule would primarily be conducted by third-party laboratories, as opposed to by drug manufacturers' in-house laboratories. According to our understanding (FDA does not provide readily accessible data on this issue), most third-party laboratories, which are also referred to as independent laboratories, in the U.S. and Canada do not have an FDA inspection history. FDA would typically only inspect an independent drug testing laboratory if the laboratory has been serving as a third-party pharmaceutical quality control laboratory for a drug manufacturer.

Before FDA finalizes a requirement that laboratories conducting statutory testing under a SIP must have an FDA inspection history, FDA should first demonstrate that a significant number of such laboratories exist throughout the U.S. Otherwise, imposing this requirement may be an implacable barrier to the successful implementation of Section 804. If there *is not* a significant number of such laboratories throughout the U.S. already, that number would not change. A laboratory could not conduct statutory testing without an FDA inspection history, but FDA would not inspect the laboratory unless it is conducting statutory testing.

We also caution FDA that some third-party pharmaceutical quality control laboratories may not be willing to conduct statutory testing of drugs that are made by one or more drug manufacturers for whom they conduct quality control testing, for fear of the drug manufacturer taking their testing needs elsewhere.

We wholly support FDA's requirement that laboratories conducting statutory testing under section 804 be accredited to ISO/IEC 17025. Accreditation to ISO/IEC 17025 is effectively an industry standard for drug testing laboratories. Laboratories that are accredited to ISO/IEC 17025 are overseen by highly sophisticated accreditation bodies, they are subject to biannual inspection by those accreditation bodies, and they risk losing their ISO/IEC 17025 accreditation if they do not continue to meet the requirements of ISO/IEC 17025. Further, the

requirements of ISO/IEC 17025 are generally either equivalent to or exceed the requirements that apply to drug testing laboratories (e.g., 21 CFR § 211.160 and 211.194).

H. SIP sponsors should be allowed to tailor their corrective actions to the problem. Requiring the SIP Sponsor to suspend the entire SIP if they determine any aspect of the SIP does not meet an applicable requirement of the FDCA, FDA regulations, or SIP is unduly burdensome and overbroad. Unless the problem affects consumer safety or program integrity, corrective action should be allowed to remedy identified concerns.

Proposed § 251.18(a) provides that 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 FDCA, FDA regulations, and the authorized SIP, the SIP Sponsor must immediately stop importation of all drugs under the SIP.

This provision is overbroad and is likely unenforceable because of its vagueness. For example, under this provision a SIP Sponsor's discovery that a single drug capsule is degraded would require the SIP-sponsor to suspend all importation under the SIP, of all drugs and across all supply chains, for some unspecified period of time. We recommend this provision instead provide that if at any point a SIP Sponsor determines that a drug, manufacturer, Foreign Seller, Importer, qualifying laboratory, or other participant in or element of a supply chain in the authorized SIP does not in fact meet all applicable requirements of the FDCA, FDA regulations, and the authorized SIP, such that the safety of drugs imported through that supply chain may be adversely affected, the SIP Sponsor must immediately stop importation under the SIP of all drugs so affected by the failure.

The proposed requirement also has no direct basis in section 804 and goes far beyond what is necessary to ensure no additional risk to the public's health and safety. For comparison, the DSCSA requires manufacturers, wholesale distributors, repackagers, and dispensers (including those participating in a SIP), if they determine that a drug in their possession or control is inauthentic, potentially harmful, or was the subject of a fraudulent transaction, to take certain corrective measures such as quarantining and disposing of the product and notifying FDA and its trading partners,¹⁴ but nothing approaching the immediate shut down of all their commercial activities.

Under our proposed revision, a SIP Sponsor could, for example, limit the suspension of importation to specific implicated supply chains. Further, the SIP Sponsor would still be required under the rule to notify FDA and demonstrate to FDA that importation has in fact been

¹⁴ See, e.g., FDCA section 581(8) and sections 582(b)(4)(B), (c)(4)(B), (d)(4)(B), and (e)(4)(B).

stopped. Under such circumstances it would be illogical for a SIP sponsor to risk their entire SIP by implementing an inappropriately narrow importation cessation.

Additionally, proposed § 251.18(a) appears to be incomplete because it does not specify under what conditions importation can restart. We recommend this provision specify that the SIP Sponsor may restart the importation when all such participants and elements of the supply chain in the authorized SIP are back in compliance with the FDCA, FDA regulations, and the authorized SIP.

I. Categorically excluding drugs subject to Risk Evaluation and Mitigation Strategies (REMS) from being eligible for importation under a SIP ignores the fact that REMS vary widely in their requirements. Many REMS could be implemented effectively under a SIP with no additional risk, thereby providing U.S. consumers with a lower cost drug that FDA would have otherwise categorically prohibited from importation under a SIP.

Proposed 21 CFR § 251.2 provides that a drug subject to a Risk Evaluation and Mitigation Strategy (REMS) (under section 505-1 of the FDCA) cannot be imported under a SIP. This would be unnecessary and an unduly burdensome categorical prohibition, as REMS vary widely in their requirements and some could be implemented effectively for a drug imported under a SIP.

A REMS is a drug safety program that FDA can require for certain medications with serious safety concerns, to help ensure the benefits of the medication outweigh its risks. There are different kinds REMS, ranging from requiring, for example, that the drug include a medication guide, to more complex requirements such as requiring that healthcare providers and pharmacists receive a special certification and follow specific requirements in order to prescribe or dispense the drug. Notably, none of these programs are affected by the source of the drugs, whether imported by the NDA sponsor or imported under a SIP. Many safety concerns addressed by REMS are a function of the drug, not its source or its supply chain. Moreover, REMS under a SIP may even be stronger than they would be otherwise because the SIP-Sponsor would have an interest in ensuring its success. Prohibiting all drugs subject to a REMS is simply unnecessary and overly burdensome.

Consider Zydelig, as an illustrative example. Zydelig is an expensive prescription drug approved by both FDA and Health Canada for treating certain types of cancer when other cancer treatments have failed. The REMS for Zydelig consists of a communications plan, implemented by the NDA holder, directed towards healthcare providers in the U.S. who are likely to prescribe Zydelig.¹⁵ Importing Zydelig under a SIP would allow persons in the U.S. who have been

¹⁵ The full REMS for Zydelig is available online here through FDA's website:
https://www.accessdata.fda.gov/drugsatfda_docs/rems/Zydelig_2018_03_22_REMS_Full.pdf

prescribed the drug to purchase it from a U.S. pharmacy at lower cost,¹⁶ without imposing any additional risk that healthcare providers who prescribe Zydelig would not be subject to the REMS communications plan.

Instead of imposing a blanket prohibition on the importation of drugs subject to REMS, FDA should determine on a case-by-case basis whether importation of a specific drug subject to a REMS would impose an additional risk to the public's health and safety simply because it would be imported under a SIP. Generally, REMS have nothing to do with the supply chain for the drug prior to its importation to the U.S., and importation of the drug under a SIP would not undermine compliance with the REMS. For example, a REMS that requires a medication guide to be included with the drug can be complied with under a SIP at the relabeling step with no additional risk to the public's health and safety. Additionally, many aspects of REMS are implemented at the pharmacy level, and there is no reason to believe a pharmacy would not comply with a REMS just because the drug was imported under a SIP. And to reiterate the above example, a REMS requiring a communication plan may be implemented separately from importation of the drug product under a SIP with no additional risk to the public's health and safety. At the very least, this category of drugs deserves a case-by-case analysis by the FDA.

J. Allowing SIPs to automatically terminate after two years if not proactively extended by FDA would set SIPs up to fail by discouraging investment and participation in the SIP.

Proposed § 251.6(a) states that, “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.” Proposed § 251.8(e) further provides that FDA may refuse to grant an extension of the authorization period for a SIP “in its sole discretion”. Both provisions are unnecessary and would mean that a SIP would terminate in the face of inaction by FDA.

Section 804 and the proposed rule provide FDA with substantial authorities and tools to assess, monitor, and suspend or terminate a SIP for actual cause at any time. States and various industry participants in the U.S. and Canada are and will be investing substantial resources to propose, establish, implement, and maintain a SIP. Allowing a SIP to terminate after two years for no reason other than FDA’s inaction is unreasonable. Although we can see justification for FDA to require SIP sponsors to recertify their SIP at some frequency (perhaps every two years),

¹⁶ Our preliminary research indicates that Zydelig costs roughly \$85 per tablet in Canada¹⁶ and \$195 per tablet in the U.S. (see “Final Recommendation for Idelalisib (Zydelig) for Chronic Lymphocytic Leukemia,” pCODR Expert Review Committee, 2015, at p. 8, and Zydelig Prices, Coupons and Patient Assistance Program,” drugs.com (at <https://www.drugs.com/price-guide/zydelig>)).

the continuation of the SIP should be presumed unless proactively terminated by FDA or the SIP Sponsor.

K. The final rule should rely as little as possible on requiring manufacturers to take certain actions and make certain disclosures. Manufacturers are likely to fight these requirements and delay as much as possible. The rule should primarily rely on other measures where possible to achieve the same aims. FDA must also be prepared to provide any necessary information that a manufacturer refuses to provide and to take any other action against the manufacturer as appropriate.

We recommend the final rule rely as little as possible on mandating drug manufacturers take certain actions and make certain disclosures to SIP participants. In this regard, the proposed rule goes beyond what is required by section 804 of the FDCA. For example, the proposed rule would require manufacturers to attest that drugs to be imported under a SIP meet all of the requirements of their approved NDA or ANDA, to confirm the manufacture dates of all drugs that will be imported under a SIP (proposed § 251.5(c)(4)(xii)), and to provide the U.S. Importer with documentation of the manufacturer's sale of the drug to the Canadian Foreign Seller (proposed § 251.14(b)). We expect manufacturers will strongly resist such requirements. Although manufacturers would face fines and potential criminal penalties for failure to comply with such provisions, manufacturers may accept fines as a cost of doing business and may test FDA's willingness to pursue criminal penalties to enforce those provisions. The final rule should primarily rely on other measures where possible to achieve the same aims.

For example, we recommend that proposed § 251.5 specifically provide, similar to proposed 21 CFR §§ 251.13 and 251.16, that if the manufacturer has not transmitted the attestation described by proposed § 251.5(c)(4)(xii) to the U.S. Importer in a timely fashion and if such information is available to FDA, FDA may transmit information that is necessary for the SIP Sponsor and U.S. Importer to confirm, subject to FDA's review and verification, whether the drug 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. Between the SIP Sponsor's and Importer's information about the drug proposed for import and FDA's information about the drug as provided in the NDA or ANDA, it should be possible for the U.S. Importer and FDA to confirm the elements described by proposed 251.5(c)(4)(xii)(A) through (E).

FDA should also take other measures under its authority if the manufacturer, for example, refuses to confirm the manufacturing dates of the drug (as would be required by § 251.5(c)(4)(xii)(D)) or refuses to provide transaction documents that it provided to the Foreign Seller (as would be required by proposed § 251.14(b)). In such a situation, for example, FDA

should leverage its inspection authority under section 704 of the FDCA to require the manufacturer to show FDA the applicable manufacturing and transaction records.

FDA should also consider the manufacturer to have refused to provide information required by the rule if the manufacturer does not appear to be acting in good faith or is otherwise being unreasonably uncooperative. For example, FDA should consider the manufacturer to have refused to provide information required by the rule if the manufacturer claims that it cannot provide the attestation required by proposed § 251.5(c)(4)(xii)(D)) because at least one aspect of the attestation would be untrue, but the manufacturer does not provide any additional information that would allow the SIP Importer, SIP Sponsor, or FDA to verify the manufacturer's claim.

L. The final rule should not include duplicative Adverse Event and ICSR Reporting Requirements and Recall Requirements. Further, it would be inappropriate to establish a novel “medication error” reporting requirement only for SIPs. This important issue should be addressed throughout the market and not limited to SIPs.

1. Duplicative and Ineffective Adverse Event and ICSR Reporting Requirements

Many of the post-importation adverse event, “medication error”, and Individual Case Safety Reports (ICSR) reporting requirements of proposed § 251.18 unnecessarily duplicate existing adverse event and ICSR reporting requirements or are otherwise inappropriate methods of monitoring and addressing any issues related to supply chains. Accordingly, much of the costs that would be imposed on SIPs by proposed § 251.18 are unnecessary.

First, we note that if FDA’s intent in requiring SIP participants to submit adverse event reports is to identify and address adverse events that were or may have been caused by SIP participants, it would be an inefficient and ineffective approach. The intent and function of adverse event reporting requirements for drugs, as long recognized by both FDA and industry, is to “offer further insight into the benefits and risks of the product” and allow for the evaluation of that information “to ensure the safe use of these products”.¹⁷ The benefits and risks of the product are wholly related to a drug’s development, manufacturing, and the content of the product’s approved labeling, not the products’ supply chain. SIP participants (e.g., wholesale distributors, importers, and pharmacies) have no control over the development, manufacturing, and the labeling content of drugs.

Second, we are concerned that proposed § 251.18(d) appears to impose the broad and vague requirement that Importers must submit reports of “all adverse events and medication errors associated with the use of their drug products imported under [a SIP]”. This would

¹⁷ Final Rule: “Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements”, 79 Fed. Reg. 33072 (June 10, 2014).

essentially be an impossible requirement, as it assumes the Importer either be omniscient or establish an extremely burdensome reporting requirement framework for all actors in the SIP and in the state (including physicians and patients) who interact with drugs imported under the SIP. Thankfully, the preamble explains that the proposed reporting requirement at § 251.18(d) would apply to such adverse events and medication errors “about which they [(the Importer)] obtain or otherwise receive information” (84 Fed. Reg. at 70821). This clarification from the preamble should be appended to the end of § 251.18(d) to keep the requirement from establishing an unrealistic and unprecedented expectation and to avoid a conflict between the text of the requirement and FDA’s stated intent for the requirement.

Third, we are concerned that the proposed requirement at § 251.18 to require, in pertinent part, SIP Importers to submit adverse event reports, ICSRs, and field alert reports, and to do so to both FDA and the NDA or ANDA holder, would lead to confusion through excess and duplicative reports. FDA regulations already require the NDA or ANDA holder to submit adverse event reports and ICSRs to FDA and already require the manufacturer, packer, and/or distributor specified on the label to submit adverse event reports and ICSRs to FDA, either directly or through the NDA or ANDA holder. By law, the label must specify the manufacturer, packer, or distributor of the drug (21 CFR § 201.1), so there will always be an entity to which users of drugs imported under a SIP can report adverse event reports and ICSRs, and that entity would then submit those reports to FDA. Requiring the SIP Importer to submit all received adverse events reports and ICSRs to both FDA and the NDA or ANDA holder will impose undue costs and result in duplicative reports. Further, these additional requirements would be wholly unnecessary if the SIP Importer is the distributor or relabeler/repackager specified on the label of the drug. Importantly, “avoid[ing] unnecessary duplication of reports” is an explicitly stated goal of the existing adverse event and ICSR reporting requirements (see 21 CFR 314.80(c)(1)(iii)).

If these reporting requirements imposed on the SIP Importer are meant to ensure that FDA can determine whether an adverse event report or ICSR relates to a drug imported under a SIP based on who is submitting the report, the requirements are largely unnecessary in that respect as well. Serious adverse events reports and ICSRs are required to specify the drug’s National Drug Code (NDC) number (see 21 CFR § 329.100(b)), which would clearly identify the drug as having been imported under a SIP. Further, the labels of all drugs imported under a SIP would feature the proposed statement that the drug was imported under a specific SIP, so any adverse event reports are likely to specify that the drug was imported under a specific SIP (as FDA recognizes at 84 Fed. Reg. at 70820).

Further, the label or labeling of all drugs imported under a SIP, in accordance with 21 CFR § 209.2, will feature a phone number that consumers can use to report any perceived drug side effects to FDA. FDA also provides an [easy-to-use portal](#) that health professionals, consumers, and patients can use to voluntarily report observed or suspected adverse drug events.

A SIP Sponsor could commit to publicizing this portal as part of its SIP outreach efforts to pharmacists, healthcare providers, and patients.

Ultimately, however, imposing any adverse event reporting requirements on SIP participants who are not already required to do so under 21 CFR 314.80 is likely to lead to confusion and to less useful adverse event reporting overall.

2. It would be inappropriate to require only SIPs to comply with a novel “medication error” reporting requirement.

FDA proposes at § 251.18(d) that SIP Importers must submit “medication error” reports to FDA and importers. The proposed rule at § 251.2 would define “medication errors” as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in control of a healthcare professional, patient, or consumer” and further provides that the “medication error may or may not result in an adverse event.”

There is currently no legal requirement for any entities to report “medication errors” that do not result in an adverse event (as would be required by proposed §§ 251.2 and 251.18(d)). FDA first attempted to require the reporting of medication errors in 2003, via a proposed rule published at 68 Fed. Reg. 12405 (March 14, 2003). The proposed rule was soundly rejected by industry on multiple grounds and FDA later withdrew it. Reviving the requirement now for the purpose of applying it only to SIPs is both substantively and procedurally inappropriate.

The definition of “medication error” at proposed § 251.2 is essentially the same definition of “medication error” FDA proposed in 2003.¹⁸ FDA received at least 181 comments on its proposed 2003 rule (many of which are not publicly available via www.regulations.gov). Rather than have us state here all the reasons why such a requirement is ill-advised, we ask that FDA revisit the docket for the 2003 proposed rule (docket FDA-2000-N-0108) and consider those comments to be incorporated by reference here. For example:

- The Federation of American Hospitals (FAH) commented that its members had “grave concerns” that “aspects of FDA’s proposal will prove to be so onerous that the reporting of adverse drug experiences will be discouraged, rather than encouraged, thus lessening the amount of information available to FDA” and that it “may result in the reporting of ‘medication errors’ which FDA has no legal ability to resolve.”¹⁹
- The Dartmouth Hitchcock Medical Center expressed a “vehement objection” that the proposed rule would take FDA “into oversight of the practice of medicine”, which is “beyond the purview of the agency.”²⁰

¹⁸ See the definition of “medication error” at proposed 21 CFR § 600.80(a), published at 68 Fed. Reg. at 12487.

¹⁹ Federation of American Hospitals, Comment to Docket 00N-1484, October 7, 2003, at p. 1.

²⁰ Dartmouth Hitchcock Medical Center, Comment to Docket No. 00N-1484, July 31, 2003, at p. 1.

- Bayer HealthCare Pharmaceuticals objected to the definition of “medication error” as being overbroad and potentially crossing over into the regulation of the practice of medicine, and recommended that the definition instead be limited to “only those problems resultant from product characteristics (e.g., labeling) that are within the control of a company.”²¹

Here, as in 2003, FDA’s proposed definition of a medication error is broad and will direct the larger controversy about the provision to SIPs alone. The issue of medication error is a systemic one, not unique to a SIP, and should not be applied exclusively to it.

Further, requiring only SIP participants, and not parties outside of SIPs, to report medication errors would be unfair and arbitrary. FDA is currently working on revising and re-proposing the 2003 medication error reporting rule, which will address many of the same definitions and standards.²² If FDA can establish a comprehensive regulation for reporting medication errors, via that rulemaking, FDA could apply such requirements in a fair manner to SIP and non-SIP participants alike. To establish such requirements now only for SIPs is substantively and procedurally inappropriate.

3. Duplicative recall requirements

We also have concerns that some of the proposed requirements regarding recalls are unnecessarily duplicative.

First, proposed § 251.18(e) would require the SIP Sponsor to monitor FDA’s recall website for recall or market withdrawal information relevant to the drugs imported under the SIP, with seemingly no allowance for the State to delegate this task to the Importer(s), who will typically already have systems and infrastructure in place to conduct this monitoring (and who would likely already be conducting this monitoring anyway). Moreover, parties other than the SIP Sponsor (e.g., such as the Importer) are in a better position to immediately recall products in response to a recall announcement. We recommend proposed § 251.18(e) be revised by deleting the phrase “they must also”, which would allow for delegation of the monitoring task in accordance with an established procedure. This procedure would be provided to FDA with the SIP proposal.

On that note, FDA asks in the NPRM, “how a SIP Sponsor and co-sponsor, if any, Foreign Seller, or Importer would effectuate a recall in the U.S., given that this will be a new responsibility for these entities.” (84 Fed. Reg. at 79822). The fact is that this will likely not be a new responsibility for Foreign Sellers nor Importers. Foreign Sellers would be Health-Canada-

²¹ Bayer HealthCare Pharmaceuticals, Comment to Docket No. 00N-1484, October 2, 2003, at p. 4.

²² See the Fall 2019 Unified Agenda, RIN 0910-AA97, “Safety Reporting Requirements for Human Drug and Biological Products”.

and-FDCA-compliant wholesale drug distributors and the Importers would be FDCA-compliant wholesale drug distributors and/or FDCA-compliant and state-regulated pharmacies. Foreign Sellers and Importers would already have established recall policies in place before joining a SIP, and so having recall policies and procedures in place would not be a new responsibility for them. At most, a Foreign Seller that does not already participate in a U.S drug supply chain may need to ensure that their recall policies and procedures extend effectively to the U.S. market, although this should not be difficult since in any recall under a SIP the Foreign Seller would be working with Importers in the U.S.

Second, FDA should clarify in the final rule the extent to which FDA expects to take on a secondary recall coordination role to a primary recall coordination role of the state agency SIP-Sponsor. We suspect FDA will almost always insist on serving as the primary recall coordinator for a recall under a SIP (as FDA does for most recalls), in which case the proposed recall provisions in proposed § 251.18(e), as currently written, would likely lead to unnecessary duplication and potentially conflicting efforts by the SIP-Sponsor and FDA.

M. The severability provision is too broad, and risks the entire rule being thrown out on a technicality. It should be tailored to specifically address FDA's underlying concerns.

Proposed 21 CFR § 251.21 provides that if any provision of the rule is stayed or determined to be invalid, the remaining provisions shall not continue in effect. FDA elaborates in the preamble that, “if one or more of [the provisions in the rule] become invalid [or stayed], the rule, as a whole, would no longer adequately protect public health and therefore should be invalid in its entirety” (84 Fed. Reg. at 70822). This justification does not fully support the severability clause because it unfairly presumes that every single provision in the rule is necessary to adequately protect public health. For example, if a requirement to submit SIPs electronically, an exception to a DSCSA requirement, or a provision in the rule allowing FDA to deny a SIP for no reason was stayed or invalidated, it would not necessarily prevent the rest of the rule from adequately protecting the public health. Furthermore, FDA could require SIPs be modified to address any risk to public health that may be caused by the invalidation or stay of one or more the rule’s provisions.

Accordingly, we propose the severability provision be tailored to reflect the underlying reason for it. For example, proposed 21 CFR § 251.20 would be more appropriately revised to: *“If any provision of this part is stayed or determined to be invalid, and the stay or invalidation would cause the rule as a whole to no longer adequately protect public health, the remaining provisions shall not continue in effect.”* In a judicial proceeding involving such a severability clause, the court would likely largely defer to FDA’s judgement and expertise with respect to whether the rest of rule would no longer adequately protect public health.

N. Comments on how to estimate savings under a SIP

The FDA requested comments on “the factors that should be considered in determining whether a reduction in the cost of covered products is significant”. The NPRM mentions the potential approach of comparing the per unit acquisition costs of drugs to be imported from Canada versus the per unit U.S. acquisition costs, in order to establish savings. Although comparing such acquisition costs would provide information about the overall cost differentials between the U.S. and Canadian markets, it would not provide an accurate assessment of savings because states have to account for administrative and supply chain costs necessary to implement a SIP. In order to do so, SIP proposals should estimate a reasonable mark-up on top of Canadian acquisition costs to more accurately calculate savings after mark-up costs, and how savings would be passed through to consumers.

Supply chain costs such as repackaging, relabeling, and testing are not transparent, however. NASHP and the state of Vermont therefore consulted with experts in the drug supply chain to develop a model that purposely overestimated supply chain costs in order to determine if, even with a large mark-up, there would be significant savings from wholesale importation from Canada. Though the actual mark-up could be significantly less, allowing for even greater savings, in the concept paper submitted by Vermont to HHS in November 2019 Vermont included a 45% mark-up that breaks down into the following components:

- 20% profit for commercial entities within the supply chain,
- 15 % for repackaging and relabeling,
- 5% for testing, and
- 5% for record keeping and recall management.

Using Zytiga, a prostate cancer drug, as a case study yields the following results: the U.S. unit price is \$87.63 versus the Canadian unit price of \$21.56²³. Allowing for the mark-up necessary to implement the program would add up to 45%, or \$9.70, to the Canadian unit price, for a total of \$31.26. Even with mark-up for supply chain costs, however, the Canadian drug in this example would still be 64% cheaper than the U.S. unit price.

For the uninsured, those savings would accrue directly to the consumer at the pharmacy counter. For insured individuals however, those savings would likely accrue directly to health plans. For covered individuals, a SIP proposal should include mechanisms for passing the savings on to consumers, including options such as lowering premiums, lowering deductibles, and reducing or eliminating copays. State insurance rate review filling requirements for health

²³ The Canadian price has been converted to U.S. dollars for this example.

plan could require a demonstration of savings from plans, including how savings were passed on to consumers.

O. Comments on timelines for FDA's review of SIP proposals

The FDA requested comments on timelines for review and approval or denial of SIP Proposals. States are designing importation program proposals in response to state legislative mandates which include deadlines for submission of program proposals to the federal government.

The state timelines for submitting SIP Proposals are as follows:

- May 1, 2020 – Maine
- July 1, 2020 – Vermont
- July 1, 2020 – Florida
- September 1, 2020 – Colorado

Unless final rules are published in a timely fashion, some states may need to re-open legislative discussions and amend their laws in order to meet these deadlines with responsive SIP Proposals.

SIP Proposals should be reviewed by FDA on a first-come, first-served basis, and on an expedited basis in order to allow approved SIP Programs to initiate importation as soon as possible to bring safe and effective, low-cost drugs to American consumers.

We appreciate this opportunity to comment on this NPRM for the Importation of Prescription Drugs, and we again commend the Administration, HHS, and FDA for taking this important step towards allowing states to help their residents access affordable prescription drugs that are safe and effective. We look forward to continued engagement with the Administration, HHS, and FDA on this rule and on this important issue.

Respectfully submitted,



Trish Riley
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