Response to Colorado RFI#: UHAA 2020*13

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RFI RESPONSE 1. Would you be interested in contracting with Colorado to provide wholesale importation services from Canada? Why or why not?

No response submitted.

RFI RESPONSE 2. What factors would encourage your participation?

No response submitted.

RFI RESPONSE 3. What factors would prohibit your participation or decrease your interest in participating?

No response submitted.

RFI RESPONSE 4. Do you have locations in Canada?

No response submitted.

RFI RESPONSE 5. Do you already purchase medications from Canadian or other foreign sources?

No response submitted.

RFI RESPONSE 6. What is the breakdown by percent of your existing volume of maintenance vs specialty medications over the past 12 months?

No response submitted.

RFI RESPONSE 7. What parts of electronic track and trace requirements in the DSCSA to be required in the future have you already implemented?

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Whether or not a wholesaler currently operating in Colorado has complied with the DSCSA does not set aside whether or not the federal law's current and upcoming requirements must be complied with.

Halfway into its decade-long rollout, the DSCSA is being implemented to facilitate a single system for tracing the manufacture and chain of custody for drug products through all entities in the supply chain.

Track-and-Trace requires that the state only do business with Authorized Trading Partners, but Colorado cannot authorize trading partners who have no controlling regulatory authority in the United States.[1]

A crucial part of the DSCSA is that all entities in the supply chain only do business with Authorized Trading Partners who are licensed and regulated. However, Colorado's Board of Pharmacy cannot regulate foreign pharmacies and wholesalers. Colorado's Board of Pharmacy cannot issue a required shutdown order to Canadian entities, nor can they enter them for an unannounced or unwelcome inspection. Colorado, simply, cannot authorize Canadian entities to be trading partners without making a complete mockery of the entire pharmacy regulatory process.

As of November 28, 2018, all drug products in America are required to be serialized. Any product brought in through a Canadian importation program would have to be serialized at their manufacturing site and tracked through their entire Canadian lifespan before introduction into the U.S. supply chain. No such Canadian medical products exist, because to label them for U.S. consumption and Track and Trace would make their labels illegal to distribute to Canadians.

RFI RESPONSE 8. Do you have direct relationships with manufacturers? All manufacturers? No manufacturers? Mix of some manufacturers and other wholesalers?

No response submitted

RFI RESPONSE 9. How would the following potential requirements influence your decision to sign up for a state program? (Please state why you are supportive or opposed to each idea)

- **Separate warehouse space for Canadian stock?**
- **Creating a separate invoice/file for Canadian drugs?**
- **Requirement to obtain a separate license from the state for importation?**
- **Equal fee schedule for all pharmacies participating in the importation program**
- **Audit of financial records to ensure "substantial cost savings" to the consumer**
- **Additional inspections by the state and potentially federal level**
- **What other requirements not listed above could be a barrier?**

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1 https://www.pharmacist.com/sites/default/files/audience/Phase%201%20Checklist%20for%20Dispensers%20FINAL.pdf; https://www.fda.gov/media/106961/download

No response submitted.

RFI RESPONSE 10. What payment models would work for you?

No response submitted.

RFI RESPONSE 11. Would you be reluctant to participate in a wholesale importation program from Canada out of concern that it could impact your existing contracts with drug manufacturers or expose you to risks of retaliation from opposing market actors?

While there is no evidence of retaliation in previous attempts by states to unwisely implement Canadian importation, wholesalers take on significant legal and financial liability when they decide to import medication and circumvent the closed, secure drug supply chain.

Cost of pharmacist, pharmacy, and wholesaler financial liability

Whether covered explicitly or through hidden costs, importing medications from the Canadian drug supply will increase liability for every voluntary participant in the supply chain that handles medication. This is because when a counterfeit is discovered, the entire supply chain is often named in the resulting civil suit, as they were in the case of transplant patient Timothy Fagan[2] who got his counterfeit from a Florida-based criminal supplier. Timothy Fagan's case was also profiled in *Dangerous Doses,* Katherine Eban's book about the criminal pharmaceutical wholesale underworld in Florida during the late 1990s and early 2000s.

In the Fagan case, nearly every member of the supply chain, from the legitimate manufacturer who had nothing to do with the counterfeit to the Florida wholesalers to the dispensing pharmacy, was named in the civil complaint. Several of them didn't escape liability until the summary judgment phase of the case. The legal representation required to escape liability in these circumstances, even when there is no fault, is still significant. Supply chain entities handling Canadian imported medications will require additional liability insurance that will add to the cost of the program, either explicitly eating up savings, or less explicitly adding to the cost of the medicine before it is sold to the patient by supply chain partners.

Because these products will require separate NDC codes, they will not be able to be mixed with other medical products in supply chain inventories, and the different origin will stick out like a sore thumb to anyone concerned about liability or a class action attorney, inviting civil litigation.

RFI RESPONSE 12. What other support would you need from the State of Colorado?

No response submitted.

[2] https://www.safemedicines.org/2018/07/drug-importation-and-liability.html

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RFI RESPONSE 13. What other information do you want to share with the State of Colorado?

In the following section, we identify a number of elements that will directly impact the administrative and operational costs of Colorado's importation program in regard to patient safety.

Requirement for significant savings will severely limit the drugs available to program participants

Senate Bill 19-005 states that "(b) ENSURE DRUG SAFETY AND COST SAVINGS FOR COLORADO CONSUMERS."

Limitations in the 2003 Medicare Modernization Act (MMA) restrict what Colorado's importation plan can attempt. Two key components required by the MMA of a state's drug importation program is that:

1. patient health and safety must not be compromised; and
2. there must be substantial cost savings to American consumers.

In 2017, 90 percent of prescriptions dispensed in the U.S. were filled with generics,[3] and generic drugs in the United States are often cheaper than either the Canadian brand-name or generic version of drugs.[4] Hence, Colorado's drug importation plan will need to focus solely on brand-name drugs to find even a possibility of cost savings, severely limiting the number of potential medications that can be imported.

Additionally, the U.S. Food and Drug Administration (FDA) has been approving new generic drugs at a record rate. In 2018, over 1,000 new generics received approval or tentative approval, with 99 being first-time generic drug approvals.[5] Given the rate at which new generics are being approved, the State of Colorado will continuously need to ensure that generic drugs have not been approved and brought to market in the United States.

Cost of drug product quality testing eliminates Canadian price savings in many cases.

Senate Bill 19-005 states that "(e) SAMPLE IMPORTED PRESCRIPTION PHARMACEUTICAL PRODUCTS FOR PURITY, CHEMICAL COMPOSITION, AND POTENCY TO THE EXTENT REQUIRED BY FEDERAL LAW." The MMA requires that all imported medications be tested at FDA-approved laboratories.

The FDA knows that it costs much less to secure the supply chain than to obtain product from an insecure supply chain and attempt to "test it into safety." In a recent paper, counterfeit

[3] https://www.fda.gov/drugs/2018-office-generic-drugs-annual-report;https://www.fda.gov/drugs/first-generic-drug-approvals/2018-first-generic-drug-approvals
[4] https://www.fda.gov/drugs/resources-you/study-us-generic-drugs-cost-less-canadian-drugs
[5] https://www.fda.gov/drugs/2018-office-generic-drugs-annual-report; https://www.fda.gov/drugs/first-generic-drug-approvals/2018-first-generic-drug-approvals

researcher Dr. Kristina Acri née Lybecker identifies 24 medicines that have been discussed for importation.[6] She then studies the costs differences of medicine available from three sources that list prices: a U.S. drug search engine (Goodrx[7]), Canadian bricks and mortar pharmacies, and unlicensed and unsafe Canadian online pharmacies.

For the 24 medicines she studies in this research paper, she obtained the cost of testing from a federally regulated lab matching the requirements in the MMA. She then computes the number of tests that must be done to achieve a determination of safety for a given batch for a "representative state" 1/50th the size of the U.S. conducting an importation program.

In 16 out of 24 cases for the medicines she studied, the cost of testing to a confidence interval of 99.99% confidence and reliability costs more than is saved by buying the medication from Canada. For these drugs, the state would lose money by buying them from Canada and testing them. The state would be better off financially buying them from the existing supply chain in America.

In fact, Colorado would even lose more money because the importation from Canada also requires the infrastructure of the Canadian importation program as described above, which would include additional costs for repackaging and relabeling.

For 99.999% confident and reliability, testing far outweighs any savings a representative state might achieve.

Colorado's Board of Pharmacy cannot regulate foreign pharmacies and wholesalers without a significant corporate presence in Colorado.

One of the first challenges the State of Colorado will face is the logistics of inspecting a business in a foreign country. The complexity of inspections necessary for a drug importation program may require additional training for Colorado inspectors as these activities have typically been performed by FDA staff. The inspection team will need to be alert to process failures, product failures, failures in laboratory tests, and process changes. Microbial test results for all batches, all initial positive sterility test results and reports of investigation, all organisms isolated and source, environmental monitoring results, and investigations, monitoring of Water for Injection (WFI) systems for microbial and endotoxin qualities will need to be examined for all sterile products.

Foreign firms are under no obligation to comply with the U.S. regulations except for their commitments in applications filed with the FDA and/or for their desire to market their products in the U.S. Colorado inspectors have no regulatory authority over foreign companies so at best inspectors will be observers. If an inspection team finds significant GMP violations or data integrity problems at the foreign facility that may require additional attention, such findings

[6] https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3402784

[7] Because of the complexity of the U.S. healthcare supply chain, a price on GoodRX.com usually does not reflect what the patient pays.

should be immediately communicated to the vendor, the appropriate person within the State of Colorado, and the Secretary of Health and Human Services. There is not much that Colorado's inspectors can do or say to change how a foreign manufacturer is running their business.

Even during pre-announced inspections at pharmacies approved by the Canadian Internet Pharmacy Association, inspectors with Minnesota's drug importation program observed dozens of safety problems:[8]

- One pharmacy failed to label its products, but instead just shipped the labels unattached in the same shipping container, even when patients received multiple medications in one shipment.
- Drugs requiring refrigeration were being shipped unrefrigerated with no evidence that the products would remain stable.
- Several pharmacies failed to send any patient drug information to patients receiving prescription drugs.

However, safety and quality issues were not the only issues facing the program. Residents simply did not participate in the program anywhere close to the projected numbers. Minnesota originally envisioned filling prescriptions in their Rx Connect drug importation program for as many as 700,000 each month. In January 2005, the program filled 1,100 prescriptions. In December 2009, the month before the program shut down, only 57 prescriptions were filled.[9]

Holding foreign entities responsible for selling the State of Colorado counterfeit or substandard medication will be a particular challenge. If selling counterfeit or substandard medication is not a crime in that country, the State of Colorado will receive no help from any local authorities. If Colorado wants to prosecute an individual for their role in the sale of fake or substandard medicine, the best option would be to have that individual come to the U.S. and arrest them once they enter the state of Colorado. In the past, individuals charged with selling counterfeit or substandard medication refuse to come into the country to face prosecution; they have just waited until prosecutors cut them a good deal.

According to the U.S. Department of Justice (DOJ), from 2009 through 2014 CanadaDrugs.com sold $78 million worth of unapproved, mislabeled and counterfeit cancer drugs to doctors across the U.S.[10] On their own website, which has since been seized by the U.S. government, CanadaDrugs.com admitted to selling American patients imported prescription drugs–a practice that the FDA says is illegal–since 2001. The November 2014 indictment of CanadaDrugs and multiple subsidiaries and executives stemmed from the distribution of two lots of counterfeit cancer medications--Avastin and Altuzan--to medical practices in the United States. It alleged that the company tried to conceal the problem rather than reporting the supply chain breach to the FDA. The counterfeit Avastin and Altuzan contained no active ingredient. The DOJ spent years attempting to bring the individuals involved into the U.S. to face justice. In the end, plea

[8] https://www.safemedicines.org/wp-content/uploads/2019/03/Letter-to-Honorable-Tim-Pawlenty_-February-23-2004-1.pdf
[9] https://www.safemedicines.org/2019/03/minnesotas-rxconnect-2003-2010.html
[10] https://www.safemedicines.org/policymakers-media/canada-drugs-case

deals made in 2018 meant that not a single person spent even a day in jail, and CanadaDrugs.com paid a fine that was less than half of the total amount of counterfeit cancer drugs sold that they sold to U.S. doctors.

Cost of testing for authenticity of medicine

SB19-0005 requires that "(e) SAMPLE IMPORTED PRESCRIPTION PHARMACEUTICAL PRODUCTS FOR PURITY, CHEMICAL COMPOSITION, AND POTENCY TO THE EXTENT REQUIRED BY FEDERAL LAW."

Proper industry-standard testing for the authenticity of medication is expensive and will be a cost driver for any vendor who is awarded a contract for Canadian importation. The MMA requires that any prescription drugs imported by a state be tested at a testing facility within the U.S. that received approval from the head of HHS. Sec 804: "(4)Qualifying Laboratory--the term 'qualifying laboratory' means a laboratory in the United States that has been approved by the Secretary for purposes of this section." The State of Colorado will need to have all drugs shipped directly to the test facility(ies) so that a statistically significant sampling can be tested. If the medicines pass, they can then be shipped to Colorado for distribution.

If drugs are not tested thoroughly and consistently, counterfeit and substandard drugs will make their way into Colorado's drug supply. When Maine legalized drug importation from Canada in 2013, within 90 days, advertisements for cheap "Canadian prescription drugs" were placed in local papers. Mac McCall, the head of the Maine Pharmacists Association, ordered several medications from one of those companies.[11] The pills he received were not from Canada or any of the other Tier One countries as the law required but were manufactured in Turkey, India, and Mauritius. When he tested the pills, one only contained 77% of the stated API and a second only 58%. The third pill tested contained an unknown contaminant.

It is an industry-standard procedure to test prescription drugs against the following four methods to ensure legitimacy:

> **Assay**: assay is a critical component of the Quality Assurance (QA) process used to determine if a pill contains the Active Pharmaceutical Ingredient (API) it is supposed to and if a pill contains the amount of that API. Not having enough or any API would indicate that the pill is subtherapeutic and counterfeit.
>
> Counterfeiters often make sub-therapeutic dose medicines that evade simple testing because there is some but not enough API present. In fact, medicines tested during Maine's disastrous 2013 importation program showed up as sub-therapeutic.[12] Such counterfeits would easily fool novices armed with only simple spectrometry equipment.

[11] http://www.safemedicines.org/wp-content/uploads/Maine-Importation.pdf
[12] http://www.safemedicines.org/wp-content/uploads/Maine-Importation.pdf

Patients expecting a therapeutic effect would be at the mercy of their disease. Even worse, their physicians may believe them to require a higher dose to achieve a therapeutic effect. When that patient gets a higher dose from a non-counterfeit, the inappropriately high dose could cause injury or death.

Dissolution rate: dissolution rate is a critical component of QA and Quality Control (QC) that ensures batch-to-batch consistency of the drug's release rate within the body of the patient.[13] An incorrect dissolution rate can significantly affect the bioavailability of a drug, and hence the drug's effectiveness at treating the patient. Should the medicine dissolve too quickly or too slowly, the patient may not be able to receive the full therapeutic effect. Subsequent actions by the physician to raise or lower the dose based upon this effect could be dangerous or fatal to the patient. Dissolution rate is an industry-standard testing criteria, and cannot be revealed by simple spectrometry.

Content uniformity: content uniformity is a critical quality measure that ensures that a consistent dose of the API is maintained between batches so that the patient receives the correct dose. The API in a pill needs to be evenly distributed throughout the tablet to ensure that if the tablet is split in half, each half of the tablet has an equal dose. This is a standard measure of quality control in the area of medicine safety.

Sterility: sterility is an essential part of QC and is used to ensure that pharmaceutical and biopharmaceutical therapeutics are sterile and safe for human use. Sterility is one of the most common problems found in counterfeits. Testing from Maine in 2013 found a non-sterile counterfeit blood thinner dispensed as a Canadian medication. Sterility is challenging to achieve and adds quite a bit to the cost, which is why you see counterfeiters failing sterility tests.

Given the history of counterfeits in importation programs, testing is going to be critical to the safety of any such plan. It is also likely to add to the cost of program administration, reducing possible savings for Colorado. As such, any vendor applicant should be required to include a cost estimate for adequate spot-checking of imported medications, and any such estimate should come directly from an approved laboratory.

Cost of repackaging, relabeling, new NDC codes, black box warnings, inserts, and serialization

Medicine in Canada is labeled differently than in America and is not suitable for distribution to U.S. patients without relabeling. Labels, warnings, and inserts have evolved to their present state to maximize patient safety and minimize harm. Even experienced healthcare professionals consult product documentation on a regular basis, so it must be compliant with approved labeling, warning, packaging, warnings, and inserts in existing FDA-approved medication.

[13] http://www.pharmtech.com/understanding-dissolution-testing

An Institute of Medicine (IOM) report from July 2006 concludes that labeling and packaging issues are the cause of 33% of all medication errors and 30% of fatalities from medication errors.[14] Safety advocates constantly study adverse medical events to see if label revisions might avert errors and recommend label changes as a result.

To that end, it is literally a matter of life or death that any medication brought into the U.S. has the correct labeling and packaging.

Additionally, healthcare professionals or patients used to a specific packaging, dose, or other labels may make mistakes if presented with a Canadian version that has a different dose or other usage difference.

The cost of this step, as well as finding a vendor, will not be trivial.

Relabeling and repackaging have to be done in a facility that follows Current Good Manufacturing Practices to ensure sterility of the medicine. Additionally, the act of repackaging and relabeling is a regulated activity in both Canada and the U.S. In Canada, any entity doing this must have this activity approved explicitly by Health Canada as part of their Drug Establishment License (DEL). In America, that activity is regulated and licensed by the FDA.

Additionally, any medicine brought into the U.S. from another country's regulated supply would require the filing of a new National Drug Code (NDC) number with the FDA. This change will carry with it both costs in fees as well as responsibilities for maintenance.

Inserts and approved packaging will all have to be affixed to the product.

The product will also have to be serialized, like all drugs sold after November 27, 2018 must be serialized per requirements of the Drugs Security and Supply Chain Act of 2013. As well as being a cost driver, products brought from the Canadian market and then re-serialized will not be as trackable as products in the existing supply chain.

<u>Cost of adverse medical events from even a small amount of counterfeit product eliminates Canadian price savings in many cases.</u>

When one is on a medication to treat a disease, it is easy to forget that there is also a cost for failing to treat the disease. It is a reasonable question to ask: "If I get a counterfeit medicine by buying outside the secure U.S. drug supply chain and my disease runs amok in my body, will the resulting treatment cost me more than I saved?"

This fact is not an abstract hypothetical. Over the past five years, several Americans who went to Tijuana for cheaper weight reduction surgery acquired a treatment-resistant bacteria.[15] The

[14] https://www.nap.edu/read/11623/chapter/1#iv

[15] https://www.cnn.com/2019/01/10/health/mexico-surgery-antibiotic-resistant-infection-cdc/index.html

medical costs related to this secondary infection have far outweighed the savings they sought to achieve by leaving the regulated U.S. healthcare system and going to Mexico's poorly regulated healthcare system.[16]

Dr. Acri's paper also looked at the cost of adverse medical events that might occur should a patient taking this medication discover their medication is counterfeit.[17] When studied for a representative state 1/50th the size of the U.S., she found that in many cases (11 out of 24) the cost of an adverse medical event outstrips any savings one might see from Canadian importation rather quickly.

Dr. Acri's paper did not attempt to analyze the cost of an adverse medical event of death, though for a medication like an EpiPen, death is a significant risk.

[16] https://www.washingtonpost.com/national/health-science/they-went-to-mexico-for-surgery-they-came-back-with-a-deadly-superbug/2019/01/23/ac0ca280-1dcb-11e9-9145-3f74070bbdb9_story.html
[17] https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3402784