THE RISKS AND REALITIES OF COMMERCIAL DRUG IMPORTATION

An End-to-End Analysis of Drug Importation Policy on Patient Safety and the Pharmaceutical Supply Chain

HDA RESEARCH FOUNDATION

SUMMARY

The impact of commercial drug importation on the pharmaceutical supply chain is not well understood. This report explores proposed drug importation policy, in general and with emphasis on proposed legislation since 2013, for commercial feasibility, operational costs to the supply chain, and impact to patients.

Multiple methods were used for qualitative and quantitative analysis as described in the appendices, including expert-panel interviews, literature reviews, and quantitative data modeling.

KEY POINTS:

- *Responsible importation relies on enacted policy achieving the current standard of drug quality and safety.*
- *Significant barriers to importation exist independent of United States (U.S.) policy proposals. These include: limited supply by the small number of countries with compatible approval and safety regulations, limits on products feasible to import, and legal and exclusivity provisions covering many high-cost medicines.*
- *Products viable for importation do not align with the greatest concerns for U.S. patients (e.g., cost and access) due to limitations imposed by handling requirements, available supply, and legality.*
- *Interviews with experts suggest that enacting moderate drug importation policy will likely lead to a 5% increase in drug-related adverse events (AEs). Further, modeling and analysis of AE data predicts a significant increase in costs to patients, conservatively estimated at $200M and potentially reaching $1.4B.*
- *Collectively, patient, regulatory, and supply chain impacts suggest a minimum threshold of $1.1B to $2.9B in costs that must be funded or accounted for in revising or implementing commercial drug importation approaches.*

This analysis concludes that the current proposed drug importation policies, as written, may not provide comprehensive guidance and funding requirements to meet current safety and quality standards for drugs in the U.S. The present realities of global drug supply and permissible product scope indicate that barriers will overshadow benefit to patients in the next three to five years. Lastly, proposed importation policies likely place the integrity of the commercial supply chain at risk.

Definitions:

Commercial Drug Importation is an activity in which a manufacturer, wholesaler, pharmacy, or third party brings drugs to the U.S. that (1) were produced outside the U.S. (2) lack Food and Drug Administration (FDA) approval, and (3) lack oversight of elements contributing to product safety and quality (i.e. ingredients, labeling, manufacturing/production, and/or handling methods) in accordance with and pursuant to a FDA approval.

Drug reimportation is a subset of approved product importation: a case where drugs manufactured and approved in the U.S., but intended for sale outside the U.S., are redirected or reimported into the U.S. commercial supply chain.

This study focuses on federal, rather than state, policies covering commercial importation.[1] Personal importation by patients physically visiting overseas pharmacies is out of scope of this analysis.[2,3]

UNCLEAR PATHS FOR PROPOSED IMPORTATION POLICY

The U.S. governance of drug standards dates to 1937 and has since been evolving (Appendix II Figure 1). This is a closed pharmaceutical system where only drugs that the FDA has reviewed and approved are permitted into the U.S. The comprehensive review and approval process includes: labeling, packaging, manufacturing, clinical data, and other information. Therefore, the system can conclude that there is substantial evidence that the benefits of the drug to U.S. patients will outweigh its risks under the FDA-approved labeled conditions of use. Maintaining these standards should be a requirement of commercial drug importation approaches.

The challenge with foreign drug imports, even if they have been approved by competent, comparable foreign authorities, is that there is no guarantee that the standards for a particular drug are the same as the FDA-approved product. This poses inherent risk to the product standards of the U.S. system and ultimately, to the patient.

In July 2018, the U.S. Department of Health and Human Services (HHS) directed the FDA to develop focused drug importation options to address access challenges. The directive was specific to single-source generics with limited patient availability while respecting patents and exclusivities.[4] This action is one example of the intent to address the increasing gap in affordability of medicines and the desire to improve patient access.

This is not the first time that changes to drug importation regulations have been considered. Lawmakers have made repeat proposals for new importation policies largely since the Medicare Modernization Act was enacted in 2003.[5] Examples of these

[1] Vermont S.175 (Act 133), enacted in 2018, permits wholesale importation of drugs from Canada pending HHS certification that this would reduce costs to consumers and pose no risk to public health. Maine's LD 171, enacted in 2013, did not require HHS certification but was overturned by the Maine District Court, which contended that federal importation provisions preempt any conflicting state laws [*(Ouellette v. Mills, 2015 WL 751760 (D. Me. Feb. 23, 2015)]*

[2] Personal importation is officially permitted only under certain circumstances, including situations in which medicines are not available within the U.S.; however, the American Bar Association notes "in practice the FDA is allowing such importation even though an equivalent drug is commercially available." *(Importing Prescription Drugs Remains Risky Business Due to FDA and DEA Regulation, American Bar Association, Mar 23, 2018)*

[3] The FDA definition of personal importation *does* include importation via courier or mail, which *is* inscope, as a party outside the U.S. is shipping product to a patient. (*"Is it legal for me to personally import drugs?" FDA*)

[4] FDA Press Announcement July 2018 webpage: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-formation-new-work-group-develop-focused-drug

[5] In particular, the Safe and Affordable Drugs from Canada Act (S.61, 116th ; previously S.2549, 113th; S.122, 114th; S.64 and S.92, 115th); the Affordable and Safe Prescription Drug Act (S.97, 116th; previously S.469, 115th); the Affordable Medications Act (S.3411, 115th); the Improving Access to Affordable Prescription Drugs Act (S.771, 115th); the Personal Drug Importation Fairness Act (H.R. 934, 115th; previously H.R.2623, 114th, and H.R.3715, 113th); the Pharmaceutical Supply and Value Enhancement Act (S.3455, 114th). Proposals introduced in both chambers are referenced by Senate identifier only.

proposals can be reviewed in Appendix II Figure 2. Proposals can be classified by their level of restrictions on the scope of drug importation as: wide open, moderate, or restricted. Experts agree the moderate or restricted importation proposals are most likely to be enacted (Appendix III Figure 2). Supporters of drug importation approaches contend that they will reduce prices and other barriers to treatment for U.S. patients, citing lower prices for similarly branded and generic products in Canada and Europe.[6,7] While this intent is noted, these proposals have considerable variability and lack specificity for execution.

As recently as 2013, the Drug Supply Chain Security Act (DSCSA) established stringent requirements for electronic traceability for all supply chain stakeholders, creating a stricter standard for products entering the U.S. supply chain. As an example, these newer DSCSA requirements have not been accounted for in current proposed drug importation policy.

If not comprehensive enough to meet current standards and legislation, proposed drug importation policy may adversely affect the quality and safety of drugs and patient health. It will also impact the operations of the pharmaceutical supply chain, which acts to maintain the current high standards. Therefore, both patient health standards and execution pathways are at risk.

Appendix II Figure 1 shows importation-related proposals since 2003. Many proposals borrow language both from each other[8] and from related terms in the Medicare Modernization Act. However, these proposals vary in detail regarding execution, and have not been reviewed in depth by the Congressional Budget Office (CBO).[9] Proposals also vary in clarity of traceability, identification, labeling, and packaging requirements.

DEFINING RESPONSIBLE IMPORTATION

To avoid emphasis on the terms of specific proposals and to promote an objective analysis, this report used detailed interviews with experts to determine a framework and definition for responsible importation (Appendix I and Appendix II Figure 2). Most experts agree (~80%) that as written, current drug importation proposals are not detailed enough for execution. This poses inherent risk to existing U.S. processes and standards that enable the flow of drugs to the patient (Appendix III Figure 2). Therefore, a framework for minimum requirements for "responsible" commercial drug importation (1-3) and supply chain execution (4) would include:

[6] Sentiment on this topic is visible from a variety of avenues, including the Trump administration (e.g., "Remarks by President Trump on Prescription Drug Prices," October 25, 2018), the media (e.g., " High U.S. Drug Prices Fuel Outrage, Innovation Debate: QuickTake," *Washington Post*, May 11, 2018), actions from Congress (e.g., Congress holds first hearings on insulin, high drug prices," *Reuters*, Jan 29, 2019), and indicators of public sentiment (e.g., "KFF Health Tracking Poll – February 2019: Prescription Drugs," *Kaiser Family Foundation*, Mar 1, 2019).

[7] Specific reports and studies regarding pricing levels include *Kesselheim AS, Avorn J, Sarpatwari A. The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform. JAMA. 2016;316(8):858–871.*, and data from the Canadian Patented Medicine Prices Review Board (e.g., "Annual Report 2017," Patented Medicine Prices Review Board)

[8] For example, the Safe and Affordable Drugs from Canada Act has been reintroduced several times since 2014 (S.61, 116th; previously S.2549, 113th; S.122, 114th; S.64 and S.92, 115th). The text of the Affordable and Safe Prescription Drug Act (S.97, 116th; previously S.469, 115th) can also be found within the Affordable Medications Act (S.3411, 115th) and Improving Access to Affordable Prescription Drugs Act (S.771, 115th)

[9] "Preliminary Estimate – S.469, the Affordable and Safe Prescription Drug Importation Act (as introduced)." Congressional Budget Office, July 2017

1) Country of Origin: Comparable regulatory standards and supply conditions;

2) Product Categories: Products capable to be imported based on chemical make-up, stability, non-FDA oversight, and handling requirements;

3) Legal and Competitive Status: Transactions that abide by exclusivity, active patents, and other legal considerations; and,

4) Supply Chain Interaction: Achievement of review, tracing, and monitoring and management per the stipulations for supply chain stakeholders.

As outlined above, experts in this study recommend these minimum requirements to define "responsible importation," or importation proposals that would preserve current quality and safety standards.

COUNTRIES MATCHING U.S. REGULATORY STANDARDS HAVE LIMITED SUPPLY OF VIABLE AND NEEDED MEDICINES

Secondary research and modeling quantified the requirements for responsible imports.

Findings suggest that the supply of importable products is limited and that these products may not align to areas where U.S. patients experience the greatest difficulties with cost and access. Successful importation also depends on foreign governments' willingness to facilitate exports. Most in-scope products are expressly intended for consumption in their own market, and some sources suggest that not all countries will support exportation to the U.S.[10]

> ***"Foreign countries [will not] allow their local supply to be skimmed off, only to create local shortages of important medicines."***
>
> *- Dr. Scott Gottlieb, former FDA Commissioner* [17]

Country of Origin: Canada and the five leading economies of the European Union (EU5: Germany, the United Kingdom, France, Italy, and Spain) are the most viable sources of drug imports, as their regulations are most comparable to U.S. standards and their geographic distance might enable efficient transport. These criteria are based on expert recommendation of each country's comparable regulatory approaches, limits of transport, and analysis of their potential available supply (Appendix II Figure 4).

Product Categories: Viable products would likely be limited to oral, small-molecule drugs (Appendix II Figure 5). Biologics would be difficult and costly to import outside the current supply chain due to product complexity and handling requirements. Some proposals also exclude biologics and complex agents outright.[11] Controlled substances would also be excluded, as they are regulated separately by the Controlled Substances

[10] Lack of overseas willingness was identified as a challenge by Dr. Scott Gottlieb, FDA Commissioner 2017-2019, in a 2016 contribution to *Forbes*: "foreign countries [will not] allow their local supply to be skimmed off, only to create local shortages of important medicines." The Canadian Minister of Health for 2008-2013 previously proposed such restrictions, and voiced opposition to drug export in a 2017 contribution to the Washington Post. *Gottlieb, "What Trump should Have Said on Drug Prices," Forbes, Mar 4, 2016; Aglukkaq, "Dear Bernie Sanders: Canada is not the United States' drugstore," Washington Post, May 12, 2017*

[11] For example, The Safe and Affordable Drugs from Canada Act (S.61, 116th), the representative policy for the moderated scenario

Act of 1970.[12] The result is limited importable product supply, with little alignment to categories of need, like products of highest price and limited access.

Legal and Competitive Status: Importable drugs will most likely need to be chemically equivalent to those approved for U.S. patients to see significant demand. Drugs will also be viable to import only if they do not infringe upon any active U.S. patents or other exclusivity provisions[13], as the cost of potential lawsuits would deter importers from bringing in protected products. [14,15] Branded medicines that have already passed U.S. exclusivity remain in scope (Appendix II Figure 6)

Based on these three criteria, drugs representing $40.3B in Canadian and EU5 sales fall in scope for this analysis (22% of the $184.7B in total annual sales across the six included markets at local prices).

Applying these criteria to 2018 sales in the U.S. suggests that responsible imports would compete with 14% to 18% of U.S. sales in that year. It should be noted that these figures represent the full *potential* scope. Most of the $40.3B in international sales would be distributed in their own markets. Therefore, the volume of non-FDA approved drug imported into the U.S. would be constrained (Appendix II Figure 3).

Pharmaceutical Sales $Bn U.S. Dollar Sales revenue
Canada, UK, Germany, France, Spain, and Italy

Scope of Importation
Estimated 2018 Pharmaceutical Sales

Importation Requirements for Study	Ex-U.S.	U.S.
1 **Countries of Origin** Estimated 2018 pharmaceutical sales in proposed countries of origin	184.7 *(+/- 8.6)*	527.6 *(+/- 24.6)*
2 **Viable Product Category** Est. 2018 pharmaceutical sales of products within scope of import: chemical or biological makeup, controlled substance status, and feasibility of management and transport	84.8 *(+/- 3.9)*	217.8 *(+/- 10.0)*
3 **Legal & Competitive Status** Est. 2018 pharmaceutical sales of inscope products that are both equivalent to a product in the U.S. (left) or outside of the U.S. (right), and not blocked by an active patent	40.3 *(+/- 1.9)*	107.8 *(+/- 5.1)*

[12] The CSA was originally introduced as H.R.18583 (91st) and enacted into effective May 1, 1971; current rules are recorded in U.S. Code Title 21 Chapter 13. Proposals explicitly barring importation of controlled substances include the Affordable and Safe Prescription Drug Act (S. 97, 116th) and the Safe and Affordable Drugs from Canada Act.
[13] The FDA guarantees exclusivity of at least five years for brand-name drugs containing new chemical entities, seven years for "orphan" drugs that treat rare diseases and are unlikely to recover development costs, and three years for in some other circumstances. Pediatric drugs gain six months additional exclusivity. The first generic drug to successfully launch against a brand-name drug also receives six months of exclusivity under current policy. "*Patents and Exclusivity," FDA, May 19, 2015*
[14] U.S. law allows patent holders to exclude others from making, using, selling, or importing a product. However, these rights are only enforced if the patent holder acts on them. Many U.S. pharma patents also cover aspects besides physical composition. This suggests that *some* protected drugs may be able to physically enter the U.S., but would likely struggle to move through the supply chain, as awareness and ability to enforce likely increase as a drug gets closer to patients
[15] Reimportation has become more complicated following the Supreme Court's 2017 decision in "Impression Products vs. Lexmark," which established that authorized sales outside the U.S. still exhaust patent rights within the U.S. However, strategies have been proposed to circumvent this ruling, and the risk of litigation still presents a potential cost barrier.

PATIENT BENEFIT AND SAFETY IS PARAMOUNT

Although importation proposals aim to reduce prices and improve access to medicines for patients, patient benefit is not guaranteed due to the limited viable product scope. Given the product scope and supply requirements, lower-priced branded and generic products are the likeliest to be imported (Appendix II Figure 7). The pricing advantage for imports in these segments is likely too small to drive significant benefit to patients.[16]

There is inherent risk to patient safety when introducing overseas imports into the supply chain and thus permitting entry for counterfeit and other unsafe drugs. Likely challenges include inspecting and validating potential imports. Even with requirements for responsible importation, counterfeit or unsafe product can enter the U.S.

Precedent suggests that authorities are not confident enough in existing regulations to certify importation. For example, the Medicare Modernization Act permits importation from Canada if the HHS Secretary certifies that this would pose no risk to public health and safety and would create significant cost savings for patients. However, all secretaries since 2003 have declined to provide these certifications.[17,18] Four former FDA Commissioners voiced similar concerns regarding safety in a 2017 letter to Congress.[19]

With these concerns in mind, costs associated with patient safety were quantified by investigating rates of drug-related adverse events (AEs). Costs required for patients to seek AE-related treatment were also included. Expert analysis predicted an estimated 5% increase in drug-related AEs under moderate or restricted terms, due to increases in counterfeiting and other sources of unsafe product. While there is little research regarding the predicted costs of drug-related AEs due to possible enacted importation policy, available estimates and incidence data combined with expert estimates result in increases ranging from $200M (based on incidence data and estimates of cost *per AE*) to $1.4B (based on estimates for *total cost* from drug-related AEs, Appendix II Figure 11).

Any increase in AEs is challenging. This study finds a lack of tangible benefits (either for pricing or access) from commercial drug importation proposals, as written, with exception of certain restricted cases. In addition, there is little evidence that benefits from these imports outweigh the safety risks to patients. This analysis provides a glimpse into the patient impacts, and the opportunity exists to further assess the patient risk/benefit through future proposals.

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[16] This is expected generally, but not universally. For example, insulin has attracted attention due to price differences between the U.S. and Canada; while insulin's status as a biologic excludes it from most importation proposals, permissive regulations could see some importation as the price difference drives importers to look past the higher logistics costs.

[17] The Medicare Modernization Act directs HHS Secretaries to permit "pharmacists and wholesalers to import prescription drugs from Canada into the United States[…]only if the Secretary certifies to the Congress that the implementation of this section will (A) pose no additional risk to the public's health and safety; and B) result in a significant reduction in the cost of covered products[…]" (H.R.1, 108th, Sec. 1121). All Secretaries since 2003 have declined to make this certification.

[18] Reliable estimates of potential savings are hard to come by. The Pew Charitable Trusts notes, "The Congressional Budget Office (CBO) estimated that potential savings from a similar policy - the Pharmaceutical Market Access Act of 2003, which would have allowed pharmacists, wholesalers, and individuals to import drugs from 25 countries, among them Australia, Canada, Japan, and a number in Europe - could have produced total savings of $40 billion over ten years in the U.S., including savings of $2.9 billion for the federal government […] *CBO also estimated that savings from the policy would be minimal if imports were permitted only from Canada*" (emphasis ours).

[19] Letter to Congress from Robert Califf (2016 - 2017), Margaret Hamburg (2009-2015), Andrew Von Eschenbach (2006 – 2009), and Mark McClellan (2002 - 2004), March 17, 2017. Accessed at https://healthpolicy.duke.edu/sites/default/files/atoms/files/2017_03_16_commissioners_letter_final_signed.pdf

THE FDA WILL BE RESPONSIBLE FOR THE QUALITY AND SAFETY OF IMPORTED MEDICINES

The challenge of regulating safety in a globalized and technological economy is already formidable.[20] Expert interviewees agreed that the burden of defining processes and ensuring the quality and safety of imported drugs would fall on the FDA. This means that the FDA will lead the planning and funding for responsible importation. Former FDA commissioners have echoed this sentiment.[21] Given the FDA's relationships with government and regulatory bodies in Canada and the European Union, the agency is well positioned for this task.

Despite having the technical expertise, added responsibility would increase the FDA's operational costs and overhead. Interviewees estimated that a moderate importation policy would lead to an eight to ten times increase in costs, including domestic and foreign inspection, headcount, staff training, quality assurance, and traceability technology. These increases would collectively triple the FDA's existing cost to operate foreign offices, inspect foreign facilities, and screen imports.

Quantitative analysis based on these estimates and published FDA budgets suggest that at least $270-350M annually would be required for the agency to handle these new responsibilities. This range aligns with estimates from interviewees with intimate knowledge of FDA processes[22](Appendix II Figure 8).

These additional costs and responsibilities to regulate importation would fall on an agency that is already experiencing capacity constraints. The Government Accountability Office (GAO) has reported on the FDA's activity overseas since 1998 and consistently identifies concerns with the program.[23] One recent report notes that almost 50% of overseas positions were vacant as of July 2016 and that inspections had yet to be conducted at over 1,000 facilities already involved in the U.S. supply chain.[22,23] The GAO's findings suggest that current funding is insufficient for the targeted volume of inspections. The FDA will likely need to address these deficits before expanding efforts to manage commercial drug importation.

Responsible importation should specify the processes, funding, authority, and timeline for expanded FDA oversight and ensure that adequate contingencies are in place.

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[20] The National Academy of Sciences, for example, notes that safety concerns and recalls even of U.S.-approved drugs present a challenge for the FDA (Pray and Robinson, "Challenges for the FDA: The Future of Drug Safety, Workshop Summary," National Academy of Sciences). Fraud and counterfeiting also remain global concerns, with data published by the Pharmaceutical Security Institute suggesting that worldwide incidents of pharmaceutical crime rose nearly 63% from 2013 to 2017 (Pharmaceutical Security Institute Incident Trends. Accessed April 3, 2019)

[21] Letter to Congress from Robert Califf (2016-2017), Margaret Hamburg (2009-2015), Andrew Von Eschenbach (2006-2009), and Mark McClellan (2002-2004), March 17, 2017.

[22] Additionally, a 2016 GAO report estimated $92m for foreign drug inspections in 2015; inspections of conventional and biologic drugs have collectively increased from 1139 in 2015 to 1407 in 2018, suggesting that the figure has increased since then. "FDA Has Improved Its Foreign Drug Inspection Program but Needs to Assess the Effectiveness and Staffing of Its Foreign Offices." Government Accountability Office, Dec 16, 2016; FDA 2017 and 2019 Budget Summaries

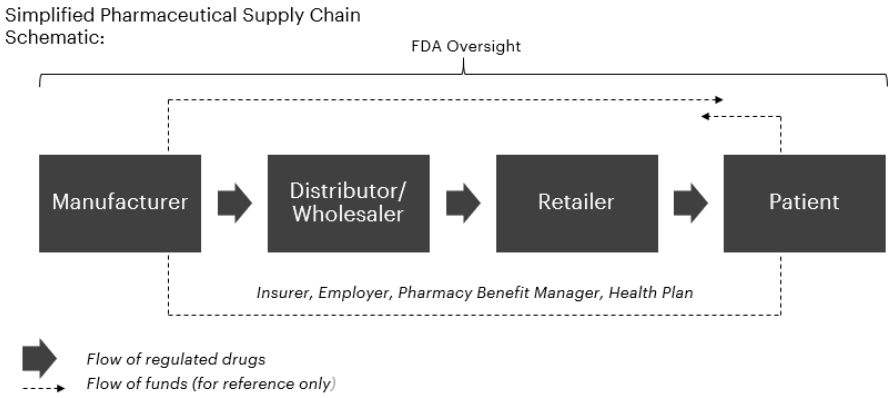
[23] The GAO has issued several reports on overseas FDA activity starting in 1998 ("Improvements Needed in the Foreign Drug Inspection Program," GAO, Mar 17, 1998) and continuing in 2008 ("Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program," GAO, Sep 22, 2008), 2009 ("High Risk Series: An Update," GAO, Jan 22, 2009), 2010 ("FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed," GAO, Oct 25, 2010), and 2016 (see previous)

This study recognizes the FDA's continued efforts to innovate, create international drug transparency, and raise quality standards. In the longer term, these global partnerships could pave the way for co-evaluation and co-approval measures for importable product.[24] This is likely a sustainable alternative to the current proposals on this topic.

THE COST TO STAKEHOLDERS EXCEEDS $1B

The standards set by regulators are implemented by supply chain stakeholders. This stakeholder analysis focuses on manufacturers, who develop and produce finished products; distributors and wholesalers,[25] who facilitate the storage and efficient transportation of product; and retail pharmacies, who dispense product and educate patients in obtaining product.

Manufacturers are important partners to the FDA to ensure product quality and patient safety. It is in their interest to preserve these standards for medicines in their market space for competitiveness and innovation. Nevertheless, some branded and generic manufacturers would see greater near-term risk, due to high overlap between their products and product scope suggested by a responsible importation policy.



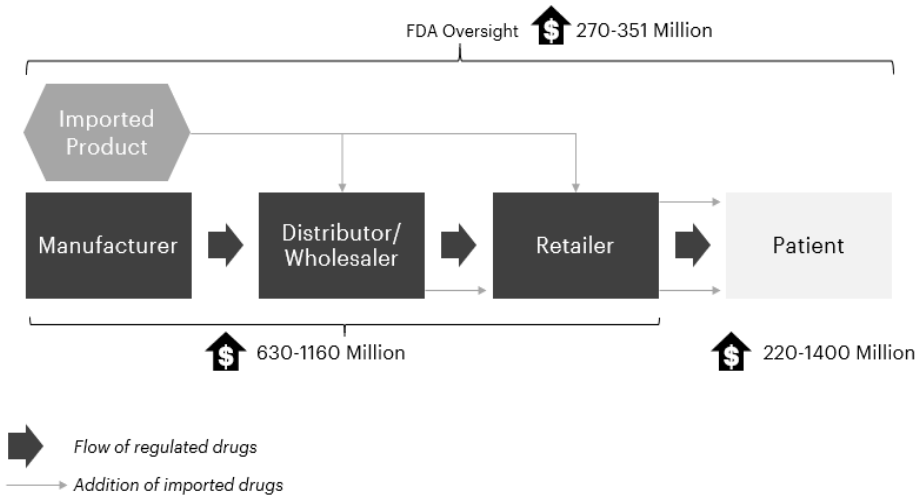
Manufacturers may also decide to protect their products and increase investments to defend patents and channels. If importers choose to challenge exclusivity provisions, litigation costs across the entire manufacturing segment could reach as high as $390-$430M per year (Appendix I Methods and Appendix II Figure 9a).

Distributors have greater flexibility and, if permitted, could choose to import product directly by collaborating with overseas suppliers. The additional costs revolve around the logistics of moving and storing imported product (e.g., warehousing and shipping). However, distributors would also need to absorb losses from product returned by retail pharmacies (e.g., recalls or overstocks); these returns likely would not be eligible for the manufacturer credits currently covering 90% of U.S. returns.[26] This analysis estimates that these would drive $240-$730M in added costs per year, depending on volume of product imported (Appendix II Figure 9b).

[24] Regarding safety, the FDA would ideally have access to foreign clinical trial reports discussing the actual effects of a drug on its biological pathway. Intellectual property confidentiality, however, may still present a significant barrier.
[25] For the remainder of the paper, "Distributor" will refer to companies in both the distribution and wholesaling sectors.
[26] 89th Edition HDA Factbook: The Facts, Figures and Trends in Healthcare (2018-2019), Table 47

Pharmacies have closer relationships with patients and may be more cautious with imports in the near term. However, costs could be incurred in protecting brand credibility and filling any gaps in compliance or pharmacovigilance. Estimated costs for regulatory oversight and supply chain stakeholders are a significant hurdle – a minimum of $900M per year – to execute a moderate importation proposal (Appendix II Figure 10). Combined with the cost to patients related to AEs, there is an estimated minimum threshold of more than $1.1B annually to overcome.

Simplified Pharmaceutical Supply Chain with Commercial Drug Importation Schematic:
TOTAL COST THRESHOLD MINIMUM: $1120 Million



SHIFTS ARE IMMINENT

If implemented, expanded importation will shift pricing models, stakeholder revenues, therapeutic dynamics, drug pricing models, and supply chain pathways.

Pricing Models: The combination of revenue disruption and impacted therapeutic categories may reshape pricing. Under manufacturers' current pricing structures, the higher prices charged in wealthier countries are used to subsidize sales in other economies and to help fund research on new therapeutics. If overseas prices spread to the U.S., manufacturers may respond by raising prices elsewhere or restricting international supply.[27] Importation could therefore interfere with the global benefits afforded by the current approach and prompt negative reactions from foreign governments concerned about their own drug prices and availability.

Stakeholder Revenues: Manufacturers (both brand and generic) may see the greatest revenue losses for a given level of adoption. For example, if 33% of in scope importable drugs replace U.S. sales, there would be an annual revenue impact of roughly $7.9B. Distributors and pharmacies may buffer lost sales of U.S. product by buying and selling the new imports. Distributors may therefore experience a smaller decrease of around $5.3B and pharmacies a decrease of around $6.1B, per year (Appendix II Figure 12).

[27] U.S. manufacturers are likely to mitigate the impact of importation on their pricing models by limiting the amount of product they sell to foreign countries and, thus, the amount of their product that could be reimported back into the U.S., at cheaper international prices.

Therapeutic Dynamics: Analysis suggests that imports will compete most heavily in the cardiovascular (62% of sales exposed), gastrointestinal (40%), and genitourinary (33%) segments (Appendix II Figure 13). These therapeutic areas differ from those identified by experts as the highest-need areas for U.S. patients, like oncology, orphan and rare disease categories. This further suggests that areas of highest viability for importation may differ from U.S. populations with the highest need and potential adoption.[28] Importantly, the issue of patient trust in medicines should be considered. Experts say that despite any decline in revenues, quality of medicines and patient safety is the mission of supply chain stakeholders.

Supply Chain Pathways: Introducing competing products may squeeze already-low margins in the generics space. This potentially reduces the number of viable players, further driving the endemic shortages and drastic price increases in the segment. On the other hand, innovative biopharmaceutical companies, may stop competing for these types of products and shift their focus to more complex and personalized drugs. Some industry leaders contend that lower prices in impacted product categories will lead to reduced investment in R&D to preserve existing margins, though other parties question the extent of this effect.[29]

Distributors may choose to maintain their traditional logistics roles or expand their capabilities and start buying directly from companies beyond U.S. governance and FDA oversight. Similarly, U.S. pharmacies could choose to partner with global pharmacies and evolve to become direct providers to patients. Non-traditional players are also likely to enter the mix. These factors change interactions across the supply chain in the longer term.

Overall, mismatches between importable supply and patient needs, potential revenue loss, and new investment requirements make commercial drug importation a challenging proposition for supply chain stakeholders. The interlock of stakeholders - which today enables appropriate delivery of medicines to patients - will face disruption.

EXPLORING ALTERNATIVES

The drug approval system in the U.S. sets a standard of quality and safety unlikely to be preserved by current proposals on commercial drug importation. For this reason, alternatives should be explored for addressing patient access and high drug costs. It should be noted that the price of a new medicine aims to reflect its value. Pricing systems try to consider therapeutic, economic, demographic, epidemiologic, and other factors that differ across countries and change over time. This flexibility aims to balance access to medicines and ongoing investment in research and development.[30]

Therefore, measures that maintain standards while reducing patient challenges and preserve flexibility for investment in innovation are preferred. For example, modifications to the "Safe Harbor" for manufacturer rebates and progress on drug

[28] It bears reiterating that some therapeutics of note, including insulin, are outside the scope of this analysis due to handling requirements and exclusion from many proposals.
[29] For example, Bach et. al. argue against the position that U.S. pricing is necessary to subsidize global R&D investment ("R&D Costs for Pharmaceutical Companies Do Not Explain Elevated U.S. Drug Prices," *Health Affairs Blog*, March 7, 2017.DOI: 10.1377/hblog20170307.059036). PhRMA and the U.S. Chamber of Commerce have expressed dissenting views (https://catalyst.phrma.org/government-imposed-price-controls-threaten-innovation-and-access)
[30] Global Pricing Flexibility for New Medicines. Global Policy and International Public Affairs, *Pfizer Inc*. October 2017

pricing transparency may be viable paths to channeling savings to patients by 2020.[31,32] The administration and Congress have proposed other initiatives targeted at price reductions,[33] approaches to increase supply and access to generic drugs,[34] and additional price transparency measures.[35,36]

The longer term challenge for the U.S. supply chain will be to strategically evolve global partnerships and regulatory mechanisms to maximize shared benefits and improve global drug approval and review standards. It is important for architects of drug importation approaches to improve their understanding of global economics of product supply, costs of aging populations, shortages, and chronic disease burden that are likely to be issues beyond U.S. borders. These must be considered for sustainable relationships with other governments.

Responsible and transparent standards, traceability, and supply are necessary for global drug standards, approval, and trade. Importantly, systems must be in place to guarantee globalized product quality and safety. Medicines are unique: patients have no easy way to ascertain the authenticity of a given drug, and supply chain disruption can have unintended consequences. Future progress should consider the terms of responsible importation as proposed and aim to address the requirements demonstrated by this study to ensure patient safety.

[31] https://www.hhs.gov/about/news/2019/01/31/trump-administration-proposes-to-lower-drug-costs-by-targeting-backdoor-rebates-and-encouraging-direct-discounts-to-patients.html
[32] Actual patient impact of rolling back Safe Harbor protections is out of scope for this analysis. However, the measure is *intended* to reduce patient cost burden.
[33] Trump Administration proposals, and part of the Prescription Drug Price Relief Act, S.102 (116th) (PDPRA)
[34] Core component of the CREATES Act (S.340, 116th) and associated proposals
[35] PDPRA HR1035 the Prescription Drug Price Transparency Act, and HR1034 the Fair Pricing Act
[36] ANPRM International Pricing Index Model for Medicare Part B Drugs; CREATES Act; Medicare Prescription Drug Price Negotiation Act (H.R. 275, 116th). Implied under public option and Medicare expansion proposals such as the Medicare-X Choice Act (S.981, 116th).

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ABOUT THE HDA RESEARCH FOUNDATION

The HDA Research Foundation is the 501(c)(3) non-profit charitable organization of the Healthcare Distribution Alliance (HDA). The Foundation serves the healthcare industry by providing research and education focused on healthcare supply chain issues. The Foundation's mission is to conduct research and disseminate information that will enhance the knowledge base, efficiency and effectiveness of the total healthcare supply chain; and to provide thought leadership to further enhance the safety and security of the healthcare supply chain through future-focused study and programming.

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APPENDICES:

APPENDIX I: METHODS SUMMARY

This analysis was conducted through a combination of literature review, expert interviews, and quantitative modeling.

The policy baseline was defined through review of existing commentary on importation published by the Congressional Research Service ("Prescription Drug Importation: A Legal Overview," 2008) and FDA summaries ("Milestones in U.S. Food and Drug Law History").

Legislative proposals were identified using the records at Congress.gov, filtering for legislative proposals in the 113th-116th Congresses with the health subject-policy area. Approximately 4,400 bill titles were reviewed to identify those related to pharmaceuticals, and those bills were then reviewed individually to identify twenty-three entries with terms covering importation, representing ten unique proposals. The terms of these policies were also leveraged to shape prompts and questions to be further validated by experts. These were direct inputs into the importation scenarios framework.

Further literature analysis was conducted via review of reports from the last five years produced or sourced via FDA.gov, HHS.gov, the Government Accountability Office, the Congressional Research Service, PubMed, the European Medical Association, and supported by other key sources of perspectives on the topics investigated throughout the analysis. The references of materials leveraged for this research are within the end-notes section.

In parallel, a group of experts were identified as respondents to structured interviews, scenario prompts for consensus development, and validation of assumptions on data (n=22 completed the interview process). These experts satisfied screening questions requirements on experience, depth of knowledge on drug importation and direct experience on elements of execution relating to drug importation. Interviewees were selected such that there was balanced representation from regulators, policy makers, manufacturers, distributors, retail pharmacies and medical advisors.

Interviews were structured, presenting the same prompts and questions to each interviewee. These interviews were conducted by phone and averaged 60 to 90 minutes each. Interviewee answers were logged and if the answer was ambiguous, the input on that question was removed from the final analysis. Interviews were conducted across five areas: regulatory baseline and proposed policy/bills, requirements for responsible importation, regulatory impacts/costs, supply chain stakeholder impacts/costs, patient impact, and general questions about the topic of drug importation.

Literature, data, and interview results were used to develop inputs into the quantitative analysis to model the impacts as outlined in this paper and the appendices.

Quantitative analysis was conducted in four phases.

First, markets of interest and countries of origin were identified by interviewees and validated based on investigation into their history of drug exports and similarity to the U.S. in both approval processes and traceability requirements. Pharmaceutical spending in these countries and in the U.S. were then estimated using data published by IQVIA.

Second, spending was segmented between branded and generic products using data from IHS Markit. These expenditures were then allocated between "in-scope" and "out-of-scope" based on product-level data from EvaluatePharma and the U.S. Drug Enforcement Agency (DEA). Out-of-scope drugs were identified based on route of administration, classification as small molecule or biologic, and presence on the DEA list of controlled substances as of December 2018. In-scope drugs were then filtered to exclude products still under U.S. patents or lacking ex-U.S. competition based on their active ingredients. In-scope dollars were further allocated between market segments based on their target markets and between therapeutic areas. An average conversion factor between international and U.S. pricing was also generated for generic and branded drugs, based on data published by the Canadian Patented Medicine Prices Review Board.

Third, revenue impact analysis was conducted using a simplified model of the U.S. supply chain, under which U.S. manufacturers sell to distributors a discount against their official wholesale acquisition cost (WAC) and distributors sell to pharmacies at a lower discount based on the same official WAC. Pharmacy pricing was simplified to a percentage upcharge against official WAC, as explicit modeling of pharmacy benefit managers was out of scope for this analysis. Total U.S. sales based on IQVIA reports were assumed to represent pharmacy revenues. Manufacturer and distributor sales were then calculated based on a 5%-off-WAC manufacturer discount to distributors and a 4%-off-WAC distributor discount to pharmacies. Potential impacts were estimated based on assumptions that overseas markets could export at most 20% of their in scope sales volume to the U.S., that all *adopted* imports would directly replace sales of existing U.S. products, and average pricing of remaining U.S. products in affected segments would decline at a level proportional to level of adoption. Distributors and pharmacies were assumed to benefit from sales of imported products. Estimates of potential adoption of imports by U.S. patients were not available, so calculations were conducted for a range of adoption levels from 0% (no patients accepting commercial imports) to 100% (patients accept all available commercial imports).

Fourth, operational cost analyses were conducted by first consulting experts as to potential areas of increased cost and then identifying cost metrics that could be used to estimate potential changes. Regulator costs were estimated using FDA budget data and GAO estimates. Manufacturer costs were estimated using product-level data from EvaluatePharma, and cost of patent litigation cases published by the American Intellectual Property Law Association. Distributor costs were estimated based on benchmarks published by the Healthcare Distribution Alliance. Patient costs were estimated using a combination of expert estimates regarding increased AE rates, data from the FDA AE Reporting System (FAERS) and estimates of per-AE and total AE-related costs identified during literature review.

APPENDIX II: REPORT FIGURES

Figures include literature and policy analysis, and quantitative modeling also informed by expert interviews outlined in Appendix III.

Figure 1: Policy Baseline[37,38]

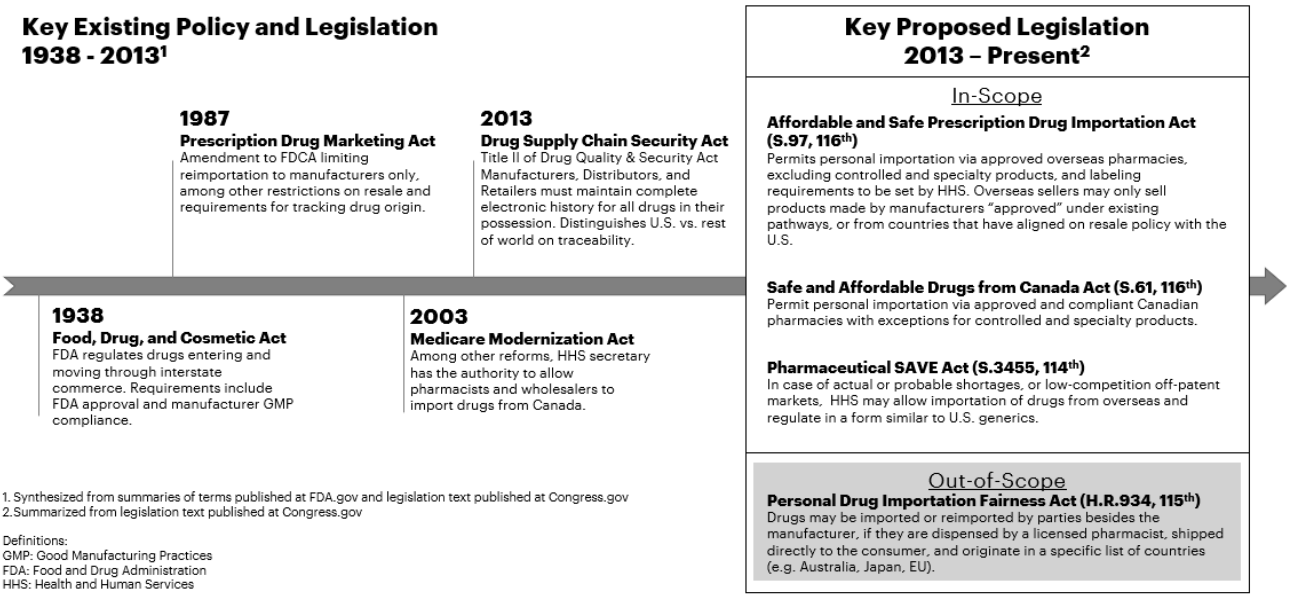


Figure 2: Importation Scenario Framework

"Wide Open"	"Moderated"	"Restricted"
Some restrictions on origin and product type, subject to specific approvals	Subject to specific and well-defined restrictions by product type and country of origin	Only in specific circumstances, subject to restrictions beyond product type and origin
Representative Policy: Affordable and Safe Prescription Drug Importation Act (S.97, 116th) • Permitted from a range of countries at HHS discretion, with options for further expansion • Few restrictions on types of products • No special requirements e.g., patent status, etc. • Importation into all parts of the supply chain, with specific licensure requirements for distributors and pharmacies	**Representative Policy: Safe and Affordable Drugs from Canada Act (S.61, 116th)** • Permitted from a set list of countries at HHS discretion, with no options for expansion • Products largely restricted to non-biologic drugs with no handling requirements • No special requirements regarding patent status, etc. • Drugs may be imported only by end consumers and in limited quantities	**Representative Policy: Pharmaceutical Supply and Value Enhancement Act (S.3455, 114th)** • Minimal country-level guidance; left to HHS discretion regarding country of origin • Products largely restricted to non-biologic drugs with no handling requirements • Specifically excludes drugs that would compete with any existing patented product

[37] Synthesized from summaries of terms published at FDA.gov and legislation text published at Congress.gov
[38] Summarized from legislation text published at Congress.gov

Figure 3: Potential Product Supply Estimation

Figure 4: Key Characteristics of Permitted Countries for Feasibility

	Canada	Germany	U.K.	France	Italy	Spain	EU (All)
History of Exporting to U.S.?	Yes (Personal)	No	No	No	No	No	No
Regulatory comparability (expert panel)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Significant Shortages (as indicator of supply challenges)?	Yes[39]	Yes[6,40]	Yes[7]	Yes[7,41]	Yes[7,8]	Yes[7,8]	Yes[7,8]
Ability to Export (Est. % volume)	*20%*	*5-15%*	*5-15%*	*5-15%*	*5-15%*	*5-15%*	*NA*

[39] Canadian sources reported as many as 400 drug shortages per month in 2017 following the rollout of the new shortage tracking system. The average duration of known shortages in 2016 was 80 days with a maximum of 414. *Donelle et al, "Assessing Canada's Drug Shortage Problem," C.D. Howe Institute, 2018*

[40] 26% of German outpatient pharmacists surveyed by ABDA in Oct. 2016 reported that shortages had caused a disruption in treatment, and that most shortages impact generics. French shortages increased 30% in 2017 compared to 2016, with similar changes seen in other European (e.g., Netherlands). *"Drug Supply Shortages in Germany," IHS Markit,* 2018

[41] Among pharmacists surveyed by the EAHP in 2018, >75% of Italian, >90% of Spanish, and>95% of U.K., French, and German hospital pharmacists responded that shortages significantly disrupted their ability to provide care or run the hospital pharmacy. >50% of Italian, >70% of Spanish, >85% of English and French, and >95% of German pharmacists also stated that these shortages happened on a weekly or daily basis. 77% of respondents across the EU found generics frequently in short supply, and 65% likewise for branded. Average shortage duration was approximately or at least 2 months for all five countries. *European Association of Hospital Pharmacists 2018 Medicines Shortage Survey*

Figure 5: Out-of-Scope vs. In-Scope Sales[42,43]

Market	Classification	Branded* (2018 est., $b)	Generics (2018 est., $b)	Total (2018 est., $b)
Canada + EU5	***Total***	***138.5 (+/- 6.6)***	***46.2 (+/- 2.0)***	***184.7 (+/- 8.6)***
	Out of Scope *Biologics, Non-Orals, Controlled Substances*	77.8 (+/- 3.7)	22.1 (+/- 1.0)	99.9 (+/- 4.7)
	In Scope *Conventional, Oral*	60.7 (+/- 2.9)	24.1 (+/- 1.1)	84.8 (+/- 3.9)
U.S.	***Total***	***381.8 (+/- 15.1)***	***145.8 (+/- 5.8)***	***527.6 (+/- 20.9)***
	Out of Scope[9,10] *Biologics, Non-Orals, Controlled Substances*	240.9 (+/- 9.6)	68.9 (+/- 2.7)	309.8 (+/- 12.3)
	In Scope *Conventional, Oral*	140.9 (+/- 5.6)	76.9 (+/- 3.1)	217.8 (+/- 8.6)

*Brand covers all products approved in the U.S. as NMEs and covers both patent-protected and off-patent branded drugs

Figure 6: Intellectual Property Considerations

	Segment	Total Inscope Sales	No Off-Patent* U.S. Competitors	Competes with Off-Patent US Product
Canada + EU5	Branded	60.7 (+/- 2.9)	35.4 (+/- 1.7)	25.3 (+/- 1.2)
	Generic	24.1 (+/- 1.1)	9.1 (+/- 0.4)	15.0 (+/- 0.7)
	Total	**84.8 (+/- 3.9)**	**44.5 (+/- 2.1)**	**40.3 (+/- 1.9)**

	Segment	Total Inscope Sales	On-Patent* or no Ex-U.S. Equivalent	Off-Patent with Ex-U.S. Equivalent
U.S.	Branded	140.9 (+/- 5.6)	114.6 (+/- 4.5)	26.3 (+/- 1.0)
	Generic	76.9 (+/- 3.1)	18.1 (+/- 0.7)	58.8 (+/- 2.3)
	Total	**217.8 (+/- 8.6)**	**132.7 (+/- 5.3)**	**85.1 (+/- 3.4)**

U.S. Patent Status and product-level sales estimates from EvaluatePharma

Figure 7: Commercial Segmentation[9,10]

	Segment	Branded	Generics	Total
Canada + EU5	**Hospital Focus** *Conventional, Oral*	4.3 (+/- 0.2)	1.3 (+/- 0.1)	5.6 (+/- 0.3)
	Mixed Focus *Conventional, Oral*	5.1 (+/- 0.3)	2.3 (+/- 0.1)	7.3 (+/- 0.4)
	Primary Care and DTC *Conventional, Oral*	15.9 (+/- 0.8)	11.5 (+/- 0.5)	27.4 (+/- 1.3)
	Total	25.3 (+/- 1.3)	15.0 (+/- 0.7)	40.3 (+/- 1.9)
U.S.	**Hospital Focus** *Conventional, Oral*	5.5 (+/- 0.2)	4.9 (+/- 0.2)	10.4 (+/- 0.4)
	Mixed Focus *Conventional, Oral*	8.5 (+/- 0.3)	10.7 (+/- 0.4)	19.1 (+/- 0.8)
	Primary Care and DTC *Conventional, Oral*	12.3 (+/- 0.5)	43.2 (+/- 1.7)	55.5 (+/- 2.2)
	Total	26.3 (+/- 1.0)	58.8 (+/- 2.3)	85.1 (+/- 3.4)

[42] IQVIA Global Outlook for Medicines Through 2021
[43] Generic and Brand shares from IHS Markit; formulation/makeup and target markets from EvaluatePharma; controlled substances from DEA

Figure 8: Estimated Regulatory Costs[44]

All cost figures in $m	Approach 1	Approach 2
Total FDA Human Drugs Budget and Fees	197.8	
Est. Domestic Inspection Allocation	107.7	80.8
Est. Foreign Inspection Allocation	45.1	72.0
Est. Import Inspection Allocation	45.1	45.1
Total Foreign + Import	90.2	117.1
Est. Cost Increase Factor	3	3
Est. Final Cost	**270.5**	**351.3**

Figure 9: Summary Costs for Manufacturers and Distributors

9a: Manufacturers	Approach 1	Approach 2
Customer Education	Insufficient Data	
Damage Control	Insufficient Data	
IP Litigation[45,46]	$390	$430
Total	$390	$430

9b: Distributors	Approach 1	Approach 2
Inventory[13,47] *Includes Product Recalls*	$210	$630
Warehousing and Shipping[13,14]	$31	$93
Customer Education	Insufficient Data	
Total	$240	$730

9c: Pharmacies
Insufficient Data
NB: No pharmacy cost increases currently identified ***Experts agreed that in the one to three year time frame, pharmacies would not see significant changes in operational cost***

Figure 10: Total Stakeholder Cost Summary

All cost figures in $m	Approach 1	Approach 2
Regulators	270	350
Manufacturers	390	430
Distributors	240	730
Pharmacies	N/A	
Total	900	1,510

[44] 2019 FDA Budget Estimates (retrospective to 2018)
[45] Bloomberg Law, American Intellectual Property Law Association
[46] IQVIA, IHS Markit, DEA, EvaluatePharma
[47] 89th Edition HDA Factbook: The Facts, Figures and Trends in Healthcare (2018-2019)

Figure 11: Patient Impact Estimates – Two Methods

	Approach 1 *FAERs; Watanabe et al*	Approach 2 *NEHI*
Adverse Events (AE) (2018) *Excludes Foreign-Reported AEs*	1.4M[48]	N/A
Average Cost per Event (2018) *Adjusted from 2014*[49]	$3.1K[50]	N/A
Cost of Adverse Events	$3.6B	$27.3B[51,52]
Estimated Increase in AEs (expert panel)	~5%	
Estimated Patient Impact	$200M	$1.4B

Figure 12: Estimated Revenue Impact by Stakeholder

Modeling assumes that all importation goes through U.S. distributors and includes the impact of both declining U.S.-origin sales and replacement sales from imported drugs. Sample cases assume that only 33% of in scope ex-U.S. product will be imported.

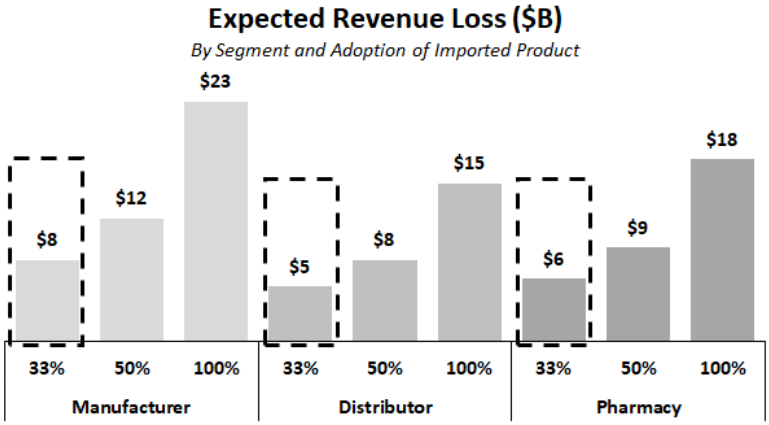


Figure 13: Therapeutic Area Impacts[53]

Therapeutic Area (TA)	"Safe" Sales	Sales "At Risk"	% of TA "At Risk"	Example "At-Risk" Products
Neurology	70.6	18.3	21%	Lamictal (Epilepsy), Abilify (Antipsychotic)
Cardiovascular	11.6	18.6	62%	Ranexa (Chest Pain); Multaq (Arrhythmia)
Genitourinary	19.6	9.7	33%	Cialis, Viagra (ED)
Gastrointestinal	11.9	7.9	40%	Nexium (GERD), Pentasa (IBD)
Endocrine	39.4	8.1	17%	Medrol (inflammatory issues)
Other TAs	289.5	22.6	7%	

Other therapeutic areas: Hematology, Dermatology, Immunodilators, Musculoskeletal, Oncology, Respiratory, Sensory Drugs (e.g., Ophthalmology), Anti-Infectives, and miscellaneous uncategorized products

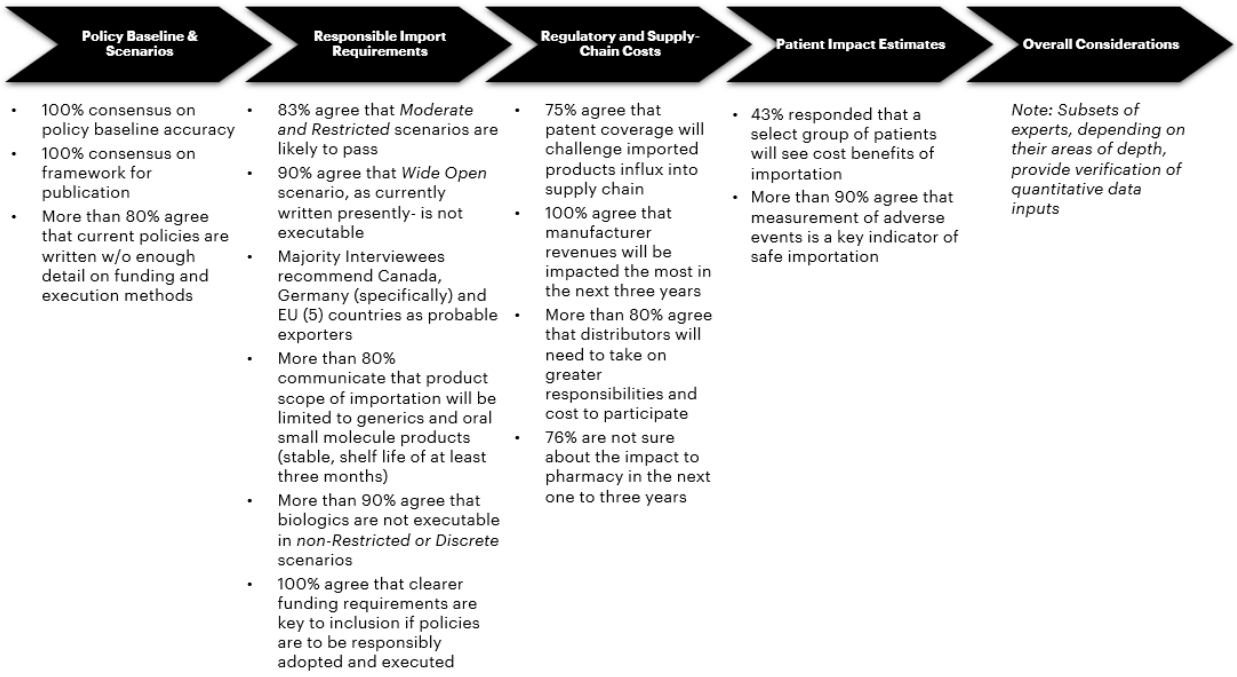
[48] FDA Adverse Event Reporting System
[49] Adjusted from 2014 to 2018 based on health expenditure values from CMS Office of the Actuary
[50] Watanabe, J. H., McInnis, T., & Hirsch, J. D. (2018). Cost of Prescription Drug–Related Morbidity and Mortality. Annals of Pharmacotherapy, 52(9), 829–837. https://doi.org/10.1177/1060028018765159
[51] New England Health Institute. Preventing medication errors: a $21 billion opportunity
[52] Adjusted from 2012 to 2018 dollars based on health expenditure values from CMS Office of the Actuary
[53] Therapeutic area data provided by EvaluatePharma

APPENDIX III: INTERVIEWEE EXPERT PANEL SUMMARY

Figure 1: Expert Credential Summary

• 22 Expert Interviews • Requirements – Minimum 20 years in relevant roles with direct authority and influence over decisions or execution in drug importation-related topics • Structured expert interviews were conducted to enable qualitative and quantitative assessment of consensus • Semi structured interviews were conducted to validate data assumptions	3	Former Lead Advisor, CDER, FDA
	3	Former Global Head, Pharmaceuticals
	2	Former Head of Pharmacovigilance, Pharmaceuticals
	1	Former CMC Review, FDA
	1	Former C-Level Advisor, Regulatory Affairs (cross-stakeholder)
	1	Former Senior Regulatory Lead, Pharmaceuticals
	2	Former Head and General Counsel, Generics Pharmaceuticals
	3	Security/Distribution/Global Ops Lead, Distributor/Wholesaler
	2	Director of Health Policy, Major Pharma Association(s)
	1	Former Director of Policy and Regulatory
	2	Chief Medical Officer, Life Science Industry
	1	Senior Health Policy Advisory to Life Science and Health Industries

Figure 2: Interview Key Points- Top 15



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