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NOT MADE IN THE USA:

THE GLOBAL PHARMACEUTICAL SUPPLY CHAIN AND PROSPECTS FOR SAFE DRUG IMPORTATION

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with Lucia Mueller

PharmacyChecker™.com

FOREWORD

What I find most interesting in this data-driven report from PharmacyChecker.com is the symbiosis that has evolved between big PhRMA and the FDA. Both the regulator and the regulated benefit from the same lie — that imports of prescription drugs from Canada, the UK and the European Union pose a grave risk to American consumers and that only the FDA can protect Americans from imports, which are inherently dangerous regardless of the country of origin. As this report documents for each of the 100 drugs on which Medicare D spends the most, the vast majority of prescription drugs sold in U.S. pharmacies are produced abroad and imported by their manufacturers to this country. What manufacturers fear most is the loss of their monopoly on importation and the exorbitant prices it secures. The manufacturers have so far succeeded in scaring most of the sick and desperate away from personal imports, whether in person or online, and in pressing for laws to prevent reputable companies like Amazon, Costco, CVS and Walgreens from commercial imports.

Both parties benefit from the lie. Manufacturers reap massive profits from monopolizing imports. As for the FDA, its budget is bolstered by being cast by PhRMA as the sole gatekeeper protecting Americans from inherently dangerous imports. As the report documents, safety regulation of pharmaceuticals in the European Union is even more stringent.

An FDA acting in the public interest would secure for the public the least expensive pharmaceuticals that can be acquired without compromising safety. It would do so by (1) identifying where prescription drugs sold in U.S. pharmacies are produced and (2) informing the public about which pharmacies licensed in high-income countries are completely safe for online imports. Ironically, these two functions are now performed by PharmacyChecker.com, although it urges the FDA to take over these tasks. I doubt that will happen unless part of FDA's funding is linked to the savings Medicare would achieve from reduced prices.

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PREFACE

I want to explain to the reader how it came to be that our little company, PharmacyChecker, set out on this ambitious project to research the manufacturing locations of prescription drugs sold in the U.S., which is a primary focus of "Not Made in the USA." You may have guessed from the title that most prescription drugs behind U.S. pharmacy counters are not made in the United States. Where drugs are made matters for many reasons, but we came to this issue initially because the prices for the same drugs sold here are much lower in other countries.

In America, millions of patients have gone without filling a prescription because they could not afford it. It's sad and unnecessary. We know that many patients have benefited from personally importing lower-cost prescription drugs. Importing medication has been a staple of prescription drug savings for decades in the United States, and yet the laws and regulations often place this practice in a legal gray area, unnecessarily curtailing access. It's my hope that this report will bring greater clarity to what needs to be done to improve the situation.

As we "go to print" on this report, we are hopeful that drafted provisions to lower drug prices, such as out-of-pocket spending caps for Medicare enrollees, inflation-based limits on drug price increases, a $35 monthly copay limit across insurers for insulin products, and Medicare negotiating prices on single-source brand-name drugs, become reality through passage of the Build Back Better Act. These provisions, while a great step forward, will not effectively help tens of millions of Americans for years to come because the pharmaceutical industry was able to stave off the larger policy lifts proposed in the Elijah E. Cummings Lower Drug Costs Now Act. As a result, importation as a means to lower prices is potentially more important than ever. The pharmaceutical industry has spent tens, if not hundreds of millions of dollars over the past two decades on lobbying, funding "non-profit" organizations, and running PR campaigns to create a false narrative that imported drugs are inherently not safe or counterfeit. It's time to end once and for all their scare tactics, show why they are so afraid of safe drug importation, and finally implement tangible solutions to lower patients' medication bills. That starts by showing unequivocally, with specificity, that many of the most expensive prescription drugs sold in the U.S. are already imported.

Lack of access to affordable prescription drugs in the United States is not a new public health crisis. At the beginning of this century, Americans, most of them over the age of 65, began turning to the Internet, Canada, and other countries, in their search for more affordable medicines. In the fall of 2002, Tod Cooperman, MD, a nationally recognized consumer healthcare expert (and founder of ConsumerLab.com), asked me if I wanted to join him in starting a company to provide information for such patient-consumers, to help them make an informed choice when purchasing medicine online for themselves and their families. So, in 2002,

PharmacyChecker began verifying the safety credentials of online pharmacies and comparing their drug prices, opening our virtual doors in April of 2003, with a niche in international pharmacy verification and safety and drug pricing. Today, PharmacyChecker fills a critical need for Americans who seek affordable prescription medications, whether through local coupons for U.S. pharmacy savings or international mail order savings, providing them with information that protects their health and safety on the Internet. Unfortunately, the pharmaceutical industry continually misinforms the public that buying “foreign drugs” is not safe. “Not Made in the USA” shows that most of the drugs sold in U.S. pharmacies are “foreign drugs.”

In 2003, a couple of weeks before PharmacyChecker launched its website, a story in the Wall Street Journal, entitled “Drug Companies Cry 'Danger' Over Imports,” reported that the lobbying group Pharmaceutical Researchers and Manufacturers of America (PhRMA) hired the public relations firm Edelman to create strategies to deter Americans from buying lower cost medicines in Canada. Using focus groups, PhRMA learned that the most effective public communications plan would use fear. Scare Americans by invoking the specter of counterfeit drugs coming from Canada. As I’ve experienced it, since that time, PhRMA has put on a master class in implementing such a strategy. Through organizations and programs funded by drug companies, such as Partnership for Safe Medicines (PSM), Alliance for Safe Online Pharmacies (ASOP), and programs of the National Association of Boards of Pharmacy (NABP), as I see it, the pharmaceutical industry has shaped the views of mainstream media on the left and the right. PhRMA’s disinformation campaign has thus made media misinformation rampant when it comes to the topic of prescription drug importation and Americans buying lower cost medicines over the Internet for their own use. (That issue is a book unto itself.) In the meantime, it got us to look very closely at the drug packaging of prescriptions sold in U.S. pharmacies and to the crux of this paper.

I’m politically liberal and inclined to be on the side of implementing more regulations dedicated to protecting public health. For that reason, it’s jarring to report how much the U.S. Food and Drug Administration seems to operate as an arm of the industry on the issue of drug importation. The FDA’s communications essentially work to inform patient-consumers and the public at large that personal imports of less expensive drugs from pharmacies located in Canada and other countries are unsafe, and, under most circumstances, technically illegal. It employs a more official sounding version of the communications strategy PhRMA came up with in 2003.

The thing is that buying medicines from pharmacies in Canada, and many other countries, is not inherently unsafe, and the law is quite flexible to allow it. That’s the truth. And it’s equally true that buying medicines from foreign countries, especially online, can be dangerous. While millions of Americans have safely filled prescription orders using international online pharmacies, way too many have ordered from dangerous, rogue websites. There’s a middle ground on this issue. It has to do with patient-focused guidance on how to find the safest online pharmacies and avoid dangerous websites. I believe that the FDA must already understand the benefits of safe personal drug importation: they know that Americans in many instances are buying the exact same drugs sold here — or safe foreign versions of those drugs — but at lower prices. Moreover, the law allows the FDA to permit personal importation of prescription drugs. I believe that for those reasons (and perhaps due to basic notions of justice and fairness), the FDA never charges, let alone prosecutes, patients who import non-controlled, prescription medicines for personal use. Doing so might be construed as human rights violations if such patients could not afford their medicines here.

In “Not Made in the USA,” we’ll show you that many of the drugs sold in U.S. pharmacies are the same medications as those ordered from pharmacies located outside the United States or equally safe foreign versions: the only difference being the prices. We’ll also show you that the data underlying FDA communications about drug importation and the global drug supply, frankly, just does not make sense. For at least 20 years, pointing to FDA data, the U.S. Government Accountability Office (GAO), the media, think tanks, consumer periodicals, academic journals — you name it! — have regurgitated the figure 80% in reference to the percentage of active pharmaceutical ingredients imported to make prescription drugs for the U.S. market. During that same period, U.S. drug supply chains were time and time again described as “increasingly global.” Then, how is it that this 80% figure remained unchanged for over two decades? In 1997, and again in 2019, the GAO referred to this same statistic from the FDA. Another statistic, that 40% of *finished* drug formulations are foreign made, had circulated for at least a decade.

Finally, after many years, a report in 2019 by the Congressional Research Service rightfully questioned the data: “A frequently cited figure is that 80% of APIs are made overseas, although questions remain about the origin of this figure.” As it happens, as we were writing this, a new GAO report came out mentioning a different figure, 76%, attributed to the FDA, to identify the number of FDA-registered *establishments* that make active pharmaceutical ingredients that are outside the United States. The percentage of factories making APIs for the U.S. is different from the percentage of our pharmaceuticals that are made outside the U.S. It may be that all this time, the 80% figure referred to establishments, not pharmaceuticals. Why didn’t Congress, the GAO, or the media, for that matter, look closer all these years?

Regardless, it has been my aim for some time to provide a data-driven report to show people exactly where the most expensive drugs are made. In 2017, PharmacyChecker began examining the countries of manufacture of popular prescription drugs. In 2018, looking at a sample of the 100 top brand name drugs, we found that 71% were made outside the United States, a far higher percentage than the FDA’s data (40%) for finished pharmaceuticals.

For “Not Made in the USA,” we employed more extensive and methodologically consistent research than the earlier efforts, which improved the accuracy of our data. We went much further than that.

The report identifies and explains (1) the laws and regulations that govern drug labeling when it comes to countries of drug origin; (2) the global nature of our pharmaceutical supply chain; (3) the inherent safety in importing medication, in particular brand name drugs, to lower drug costs; (4) the need for vigilance but balance when it comes to addressing national security threats emanating from China’s position as an exporter of pharmaceuticals and reliance on foreign pharmaceuticals generally in the wake of the COVID-19 pandemic; (5) importation proposals and activities permissible under current law, their legal framework, and prospects to substantively reform that framework to allow for large scale parallel drug importation; and (6) the political economy basis for the FDA’s perpetuation of the industry’s position on drug importation and how it’s no longer defensible.

We thought about dialing it back and just publishing the main data (drug name, where the active pharmaceutical ingredient comes from, and where it was formulated into a finished drug, along with domestic and foreign pricing). But, if you dive in all the way, it is my hope that you come out looking at these issues in a new light to better recognize public policies that are good for patients, public health, and taxpayers.

You may have noticed above I sometimes used the singular “I” and other times the plural “we.” The “we” is mostly Lucia Mueller, VP of operations and communications at PharmacyChecker, who is the lead editor and a co-author of this report. Thanks, Lucia! Our former colleague, Shivam Patel, PharmD, provided valuable preliminary research. I also want to thank Larry Gorkin for giving this a read and making some excellent suggestions. Finally, but very importantly, Jane Horvath, who pioneered the state wholesale drug importation programs, was scathing in her comments about an earlier draft, and we needed to hear them. Jane’s constructive criticism helped us make this a better paper in addressing myriad public policy issues of mutual concern.

It’s a well-established fact that affordable prescription drugs improve prescription adherence and overall health among Americans. Mostly, in this report, we aim to show how expanding access to lower-cost prescription drugs outside the U.S. could substantively alleviate the crisis of high drug costs in America.

GABRIEL LEVITT
PRESIDENT, PHARMACYCHECKER.COM

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ACRONYMS AND ABBREVIATIONS

ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
CBP	United States Customs and Border Protection
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CIPA	Canadian International Pharmacy Association
DSCSA	Drug Supply Chain Security Act
EO	Executive Order
EU	European Union
FDA	United States Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
FDF	Finished Drug Formulation
FTC	Federal Trade Commission
GAO	Government Accountability Office
GMP	Good Manufacturing Practices
HHS	Department of Health and Human Services
JAMA	Journal of the American Medical Association
MMA	Multi-market approved
MOU	Memorandum of Understanding
MRA	Mutual Recognition Agreement
MSD	Merck Sharp & Dohme Corp.
NASHP	National Academy for State Health Policy
NDC	National Drug Code
OECD	Organisation for Economic Cooperation Development
PhRMA	The Pharmaceutical Researchers and Manufacturers of America
RFP	Request for Proposal
USA	United States of America

EXECUTIVE SUMMARY

OVERVIEW

Many consumer products clearly state where those products are made. Not so for prescription medications. Where our drugs are made and where their main ingredients are sourced affects drug safety, affordability, availability, and even national security — concerns that have come to the fore as a result of the global pandemic. Yet there is too little transparency and too much misinformation surrounding the supply chain of the drugs we take.

"Not Made in the USA" investigates and details the country of manufacture and the source country for active pharmaceutical ingredients among widely used, brand name prescription drugs. The data shows that the majority of brand name prescription drugs Americans take are not made in the U.S.A., rather they are made in other high-income countries with equally — if not more — stringent pharmaceutical manufacturing capabilities than the United States. As a corollary, it becomes clear that imports of drugs from licensed pharmacies or wholesalers in many countries are no less safe — but much less expensive — than drugs purchased domestically. This is critical information in the debate on whether expansion of drug importation to lower drug prices would be effective and safe for the American consumer.

"Not Made in the USA" includes a thorough examination of drug labels as applied by manufacturers (i.e., not repackagers or relabelers) and an analysis of federal drug labeling laws along with the conflicting FDA, FDCA, and CBP definitions of a drug's country of origin. The report identifies countries of manufacture for the top 100 drugs by total expenditures in Medicare Part D in 2018. Looking at wholesale and retail channels, "Not Made in the USA" discusses the vast domestic vs. international price discrepancies of these top 100 drugs. To analyze safety issues relating to drug importation and prices, the report discusses global supply chain issues, including FDA registration and recordkeeping of foreign made drugs; brand versus generic drug supply quality concerns; and issues of national security. Finally, and in depth, the report identifies and analyzes proposed drug importation laws, regulations, and rules that could vastly improve drug affordability for American consumers and government payors.

KEY FINDINGS

- A large majority of the top 100 drugs in Medicare Part D are brand products produced outside the U.S.:
  - **68%** of finished drug formulations (FDFs)[i]
  - **78%** of active pharmaceutical ingredients (APIs)[ii]

These brand name products ranged from exceedingly expensive cancer, biologic, and specialty drugs to more widely prescribed maintenance medications.

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i Finished Drug Formulation (FDF) is the term for the final drug product prescribed to a patient by a medical professional.

ii Active Pharmaceutical Ingredients (APIs) are the key components of a medicine that produce the intended effects in the body. Since a large majority of prescription drugs sold in the U.S. are made with foreign APIs, tracking where they originate is an important public health issue.

- Almost all imported brand name drugs are made in countries with manufacturing safety practices equal or superior to those in the United States.

Similar to generic drugs, most brand FDFs and their APIs are foreign made. What differs is that most FDA-approved brand name drugs, including their APIs, are made in high-income countries with strong pharmaceutical regulations. Of the 100 Medicare Part D drugs assessed in our report, 32 were finished in the U.S.; 67 were finished in countries that have comparable to if not stronger systems of pharmaceutical manufacturing than the U.S.: the countries in the European Union, Canada, Japan, Singapore, Switzerland, and the United Kingdom. One drug, brand Neurontin (gabapentin), was formulated in India.

- Most imported brand name drugs are made in countries that are considered democratic allies of the U.S.

With one exception in our data set, all foreign countries of origin making FDA-approved, brand name drugs are democratic allies. The exception, Imbruvica (ibrutinib), included the API made in China, with the product finished in the United States. In contrast, many generic drugs are comprised of ingredients from China, indicating that national security vulnerabilities are much fewer for brand than generic drugs.

- Of those drugs from the dataset that are accessible online, average international mail order prices were 75.53% lower than average U.S. pharmacy prices. Average prices available of drugs only shipped from Canadian dispensing pharmacies were 70.18% lower than average U.S. pharmacy retail prices.

SUMMARY OF POLICY RECOMMENDATIONS FOR THE FEDERAL GOVERNMENT

- ❖ Require manufacturers to clearly identify the country of origin of a drug's API and FDF.
- ❖ Through legislation, expressly allow importation of brand name drugs by companies, other than their manufacturers, from countries known to have similarly strong pharmaceutical regulations as the U.S., subject to rational regulatory safeguards.
- ❖ Remove barriers and provide guidance to assist individual patients who seek to import brand name drugs pursuant to a valid prescription.
- ❖ End wasteful spending in Medicare by ensuring that lower cost, available generic drugs are used instead of the far more expensive brand name counterpart.
- ❖ Mandate through legislation an annual FDA report with the underlying data that shows accurate data on where our drugs are made.
- ❖ Pursue greater global collaboration and coordination:
  - ➢ toward an international agreement to better regulate and ensure the safe manufacture and high quality of APIs.
  - ➢ among democratic allies, starting with the G7 and expanding to the OECD, to mutually assess the threats from dependence on China for pharmaceuticals.

SECTION 1: INTRODUCTION

1.1. CONTEXT AND STUDY RATIONALE

The U.S. Food and Drug Administration (FDA), the agency responsible for regulating drugs sold in the U.S., does not require drug companies to include a drug's country of origin on its product label; neither for finished drug formulations (FDFs) nor their active pharmaceutical ingredients (APIs). Although the FDA is supposed to record this information as a condition of issuing a drug license, the information is not readily available to the public, and public record indicates the FDA may not adequately meet its regulatory obligations when it comes to this data. Public availability of country-of-origin information for prescription drugs is important and useful for consumers, public health experts, and centers of oversight, such as the Government Accountability Office (GAO) on matters relating to drug safety, national security, and healthcare spending. It should be of particular interest to policymakers looking toward drug importation as a means to enhance price competition and lower drug prices for Americans.

In 2010, then FDA Commissioner Margaret Hamburg, MD, said that 40% of finished drugs sold in the U.S. and 80% of their APIs were imported.[1] Those *statistics* were used repeatedly without validation or revision for many years. The 80% figure was used by the GAO as recently as 2019.[2] As far back as 1998, over 20 years ago, the GAO stated that, according to FDA data, 80% of APIs were imported.[3] These figures are commonly regurgitated in the media,[4] [5] congressional hearings,[6] [7] and academic journals[8] [9]as authoritative. Yet there is no 'hard data' that the FDA provides to support it.

It may not be the FDA's statutory responsibility to inform the public about the number of FDA-approved drugs made outside the U.S., but it is important for the public to have confidence in the FDA's own recordkeeping on this subject.

Public Citizen analyzed trade data from 2019 and found that the three top countries from which bulk pharmaceutical ingredients are imported into the U.S. are China, India, and Mexico. The next top countries from which the U.S. imports pharmaceuticals are Canada, Germany, Italy, the UK, Spain, Israel, and Ireland. Where the *volume* of the former group is larger, the *dollar value* of the latter group is much higher.[10] That is explained by the fact that the former group's products are largely for less expensive generic prescription and OTC drugs and the latter

IN THE MEDIA: WHERE IS MY DRUG MADE?

Los Angeles Times columnist David Lazarus wrote in 2018 about the lack of transparency when it comes to a drug's country of origin:

"...it's often impossible to get a fix on any aspect of the supply chain or manufacturing process. Take a look in your own medicine cabinet. More than likely, not one prescription drug has a country of origin on the label."[i]

In Health Affairs, from a 2020 post called "We Still Don't Know Who Makes This Drug," the authors echo the same conclusion:

"Under current policy, the required labeling of prescription drugs sold in the US does not disclose the name of the actual FDF manufacturer, nor the manufacturer of its APIs. Neither do the labels disclose the location of the drug's API or FDF manufacturer (although the labeling typically discloses the name and contact information of the company marketing the drug, that is, the ANDA holder.)"

group's products include many brand name drugs or the APIs to manufacture brand name drugs. While China may lead as the largest supplier of bulk pharmaceutical ingredients, many of those are for over-the-counter products, not prescription drugs, or to make less expensive generic drugs – but seldom for the APIs that go into brand name drugs.

For decades, the public debate about whether to legalize prescription drug importation has presented a false dichotomy. The debate is often framed as whether "to legalize drug importation or not to legalize drug importation." That's a false presentation of the law. Drug importation is legal. However, while there are exceptions for personal importation and special authorizations for wholesale importation, commercial (wholesale) drug importation is expressly legal but only if authorized by drug manufacturers. That protected distribution channel allows drug companies to control the U.S. price of a drug. Opponents of drug importation as a policy to lower prices have maintained this protection, in part, by misleading the public in baldly asserting that "foreign drugs" are not safe.[11] [12] "Not Made in the USA" explains and shows, with hard data, how most of our drugs are foreign already, including the most expensive ones.

1.2. Objectives and Purposes

A principal objective of "Not Made in the USA" is to provide the public with primary data on the countries of origin of brand name drugs. The central purpose of that objective is to show that a large majority of our most costly drugs are not made in the U.S. but in countries with equally strong, if not stronger, pharmaceutical regulations. The corollary objective is to show how removing trade protections on pharmaceuticals from those countries would bring down drug prices in the United States.

Other objectives for the report are to explain and demystify the overlapping federal regulations related to drug labeling; potential problems with FDA's recordkeeping; why brand name drugs are, at least to a degree, often of higher quality than generic drugs; and the real vs. exaggerated vulnerability of the U.S. to foreign drug suppliers.

Section 2: Data and Methods

The dataset of drugs for this report comes from the *Medicare Part D Drug Spending Dashboard & Data*.[13] The drugs chosen to determine their countries of origin were the top 100 drugs by total spending in 2018. Where there were generic drugs listed, we looked at the *brand name* product to assess the manufacturing origin of that drug.[iii] Eighty-five of the 100 were single source drugs with no generic availability in 2018.

The principal method for determining the countries of origin was closely reading drug labels available in the *U.S. National Library of Medicine*.[14] Where those labels were ambiguous, researchers looked to the *FDA Labeling-Package Insert* drug information.[15] In several cases, drug manufacturers were contacted directly by phone or email, and answers were recorded to obtain the information. The manufacturing location data for each drug is broken down by both the locations of the FDF and API manufacture. For example, in the case of the drug Januvia (sitagliptin), the API is made in Italy and the FDF in the UK.

iii Spending on those generic products is captured in the source data.

Data on drug prices came primarily from GoodRx.com and PharmacyChecker.com. The report compares retail drug prices available at U.S. and foreign pharmacies. Average U.S. retail prices came from GoodRx.com, and, in a few cases, Drugs.com. Average Canadian and other international pharmacy prices came from prices listed by PharmacyChecker-accredited online pharmacies on PharmacyChecker.com. The drugs for which prices were compared were those available for purchase internationally. Average *Canadian pharmacy prices* came from online pharmacies that only process international prescription orders from a licensed Canadian dispensing pharmacy. The average of *other international pharmacy prices* came from international online pharmacies that process prescription drug orders of medications approved for sale in the following countries: Australia, Canada, India, New Zealand, Turkey, and the United Kingdom.[iv]

2.1. Explanation of Dataset Focus on Brand Drugs

Concerns about the safety of the U.S. drug supply often center on generic drugs.[16] "The Geography of Prescription Pharmaceuticals Supplied to the U.S.: Levels, Trends and Implications," published in the *National Bureau for Economic Research* in 2019, takes a deep dive into the FDA's importation data, information generally shielded from the public, to shed light on the supply chain of *generic* drug products. A line from that report reveals the lack of data on brand name drugs:

> "We do not have information on the manufacturing location of branded, non-generic drugs, nor on over-the-counter non-prescription formulations."[17]

By focusing on brand name prescription drugs, this paper helps address that research gap. Understanding the supply chain and country origins of brand name drugs, in particular, is important for the following reasons, which are interrelated:

1) Their exorbitant prices in the U.S. relative to other countries
2) Their large share of all prescription drug expenditures by federal, state, and municipal payors
3) Their countries of origin are almost entirely U.S. allies and friendly trading partners
4) Misconceptions about drug importation, ones that have likely prevented regulatory reforms allowing importation that would help Americans and taxpayers spend less on prescription drugs

Identifying the countries of manufacture of brand name drugs, in addition to those of generic drugs, is highly relevant to current policy developments pertaining to drug prices and importation. Generic drugs make up about 90% of all prescriptions dispensed in the U.S. each year.[18] Yet brand name drugs account for about 80% of all expenditures.[19] An April 2021 Kaiser Family Foundation analysis found that Medicare's top-selling 250 drugs with one manufacturer (i.e., almost entirely brand name drugs) and no generic or biosimilar competitors accounted for 60% of net total Part D spending in 2019.[20]

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iv PharmacyChecker-accredited international online pharmacies process orders for non-controlled prescription drugs for patients with a valid prescription and filled by pharmacies licensed in the countries where they operate. The PharmacyChecker Verification Program online pharmacy safety standards are available at: https://cdn.pharmacychecker.com/pdf/VP+Accreditation+Standards+and+Guide.pdf.

According to research conducted by the U.S. House Ways and Means Committee published in 2019, drug prices at the wholesale level are about 75% lower on average in other high-income countries on 79 drugs that make up 60% of spending in Medicare Part D.[21] That dataset consists only of brand name drugs. For decades, federal law, with limited exceptions, has protected the pharmaceutical industry from price competition from the foreign, wholesale drug prices by prohibiting all commercial entities except for the manufacturer from importing those same drugs at lower prices.

2.2. Federal Law and Drug Labeling: Differing Definitions of an Imported Drug

We reviewed the Food, Drug and Cosmetic Act (FDCA), the Tariff Act, and the Federal Trade Commission (FTC) Act because they each can affect how a drug manufacturer labels a drug product in terms of its country of origin. The interplay of the various requirements can prove difficult for consumers and policymakers to readily ascertain where a drug was made.

The FDA, which is responsible for the enforcing the FDCA, and U.S. Customs and Border Protection, an agency with the Department of Homeland Security, play prominent roles in the importation of prescription drugs[22]:

- The FDA regulates which drugs can be imported.
- CBP, along with the FDA, regulate the physical importation of drugs.

The FDA and CBP have different definitions for assigning a country of origin to a drug. To the FDA, the country where the *final formulation* of a drug occurs, including where it's packaged, is the drug's country of manufacture.[23] The FDCA does not require manufacturers to publish the countries of manufacture on prescription drug labels or otherwise make the information public.[24]

To CBP, *the country in which the API is made* is the country of origin.[25] Therefore, to the CBP, under most circumstances, an imported drug is one where the API was manufactured outside the United States.[26] There are exceptions to CBP's definition: if a drug is *substantially transformed* during the manufacturing process regardless of where the ingredients came from, and/or when two APIs are combined into one drug formulation.[27]

Consider the drug Eliquis (apixaban). According to its label, the API of Eliquis, apixaban, is made in Switzerland, but it becomes an FDF in the United States. To the FDA, Eliquis is manufactured in the United States. To the CBP, Eliquis is an imported drug.

While the FDCA does not require drug companies to publish the countries of manufacture on prescription drug labels, the Tariff Act and the FTC Act add requirements and constraints on drug labels of imported products. [28] [29]

- The Tariff Act mandates that the country of a product's origin is printed on the labels of all imported products and is enforced by CBP.[30]
- The FTC Act prohibits false or misleading "Made in America" claims.[31]

In understanding the requirements of the FDCA, the Tariff Act, and the FTC Act, and how they work together, with access to the manufacturer's label, it usually becomes clear where a drug was made, both the FDF and the API.

2.2.1. The Food, Drug, and Cosmetic Act

The FDCA governs prescription drug licensure, which includes labeling. The law requires only that a manufacturer's drug label bear the name of the manufacturer and *any address* associated with the company. The address does not have to be where the drug was made. For instance, the location and country identified on the label can be a manufacturer's principal place of business, such as corporate headquarters, instead of the country of the factory where the drug was made. While the FDCA does not require country of origin labeling, its section on misbranding requires truthfulness in labeling, which applies to labels on imported drugs. Under the FDCA, a drug is considered "misbranded" if "its labeling is false or misleading in any particular."[32] When a drug company labels a product in violation of the Tariff Act, it may run afoul of the misbranding regulations.[33]

2.2.2. The Tariff Act of 1930

The Tariff Act of 1930 as amended requires imported products to be labeled with the country of manufacture.[34] If an imported product mentions a country on its label that is not the country of manufacture, then it must clearly add information showing the name of the country of origin. The Tariff Act is enforced by the CBP pursuant to the Code of Federal Regulations (CFR) 19 134.46:

> "Section 134.46, Customs Regulations (19 CFR 134.46) provides that in any case in which the words 'United States' or 'American,' the letters 'U.S.A.,' any variation of such words or letters, or the name of any city or locality in the United States, or the name of any foreign country or locality other than the country or locality in which the article was manufactured or produced, appear on an imported article *or its container* (emphasis added), there shall appear, legibly and permanently, in close proximity to such words, letters or name, and in at least a comparable size, the name of the country of origin preceded by 'Made in...'"[35]

In addition to the phrase "made in," if the country is preceded by the phrases "Product of," or "Manufactured by," that is the country of origin, according to CBP personnel in an email exchange with PharmacyChecker (P.J. Ghazi, personal communication, July 21, 2020). A drug manufacturer cannot list a U.S. address alone without including the country of manufacture for a drug with a foreign made API. Thus, a drug labeled solely with a U.S. address, without any marking of a foreign location, would be considered, by the FDA and the CBP, to be manufactured domestically.

Here is how this relates to our data:

- 22 of the 100 (22%) drug labels examined listed only a U.S. address.
- For those 22 drugs, we called the marketing drug companies to confirm their countries of manufacture. In that respect, under CBP's definition, 78% of the drugs examined in this research were foreign made.

2.2.3. The Federal Trade Commission Act

The Federal Trade Commission Act makes it illegal to market a product with the phrase "Made in the U.S.A.," unless "all or virtually all" the contents of the product are domestically manufactured.[36] The FTC Act's bar is very high for a company to make this claim, and this may affect the decisions of drug manufacturers not to use it.

Even though 22 drugs in the dataset were identified as manufactured domestically, both API and FDF, only two drug labels included the words “Made in the U.S.A.” It is conceivable that a drug with a domestically manufactured API, one labeled only with a U.S. address, cannot make the claim “Made in the U.S.A.'' if any of its excipients (i.e., inactive pharmaceutical ingredients) are imported.

Across many consumer goods, affixing “Made in the U.S.A.” is commonly considered a worthwhile marketing claim.[37] In the case of a patented, brand name prescription drug for which there is no alternative, the “Made in the U.S.A.” claim may not play the same role for the patient consumer. In the prescription drug market, there is far less consumer choice than in most other markets. When patients fill prescriptions at a pharmacy, they often do not have a preference or even the option of the manufacturer beyond brand vs. generic. Additionally, insurers and pharmacy benefit managers often make it difficult for patients to access a branded drug when a generic alternative is available, by requiring prior authorization, a process through which a prescriber must obtain special approval from an insurer if a brand is requested instead of an available generic.[38] In some cases, due to concerns about low quality generic or narrow therapeutic index drugs, where a generic drug from a specific manufacturer is not working for a patient, that patient or their provider may ask the pharmacy for a manufacturer-specific drug, whether it is a brand or generic.[39]

2.3. Countries of Origin of Top 100 Medicare Part D Drugs by Expenditure in 2018

In 2018, 68% of finished drug products and 78% of active pharmaceutical ingredients of the top 100 Medicare prescription drugs by total expenditures sold in the United States were imported. Those imported drugs accounted for 57% of overall spending in Medicare.

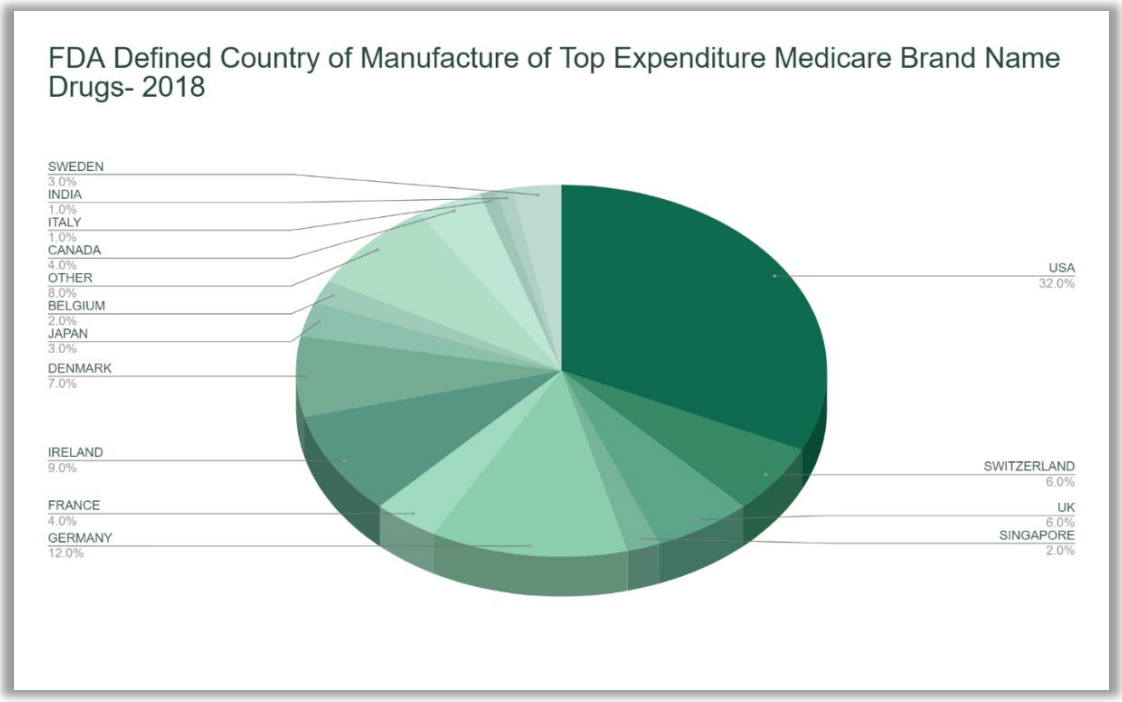
- Under CBP’s definition, **78%** of the 100 drugs examined were foreign made because the API was made outside the U.S., without regard to where the finished product was made.

- Under FDA’s definition, **68%** of the 100 drugs examined were foreign made because the finished drug was imported.

- **98%** of the drugs assessed were made in countries that have comparable if not better systems of pharmaceutical regulations to the U.S. according the CBP.

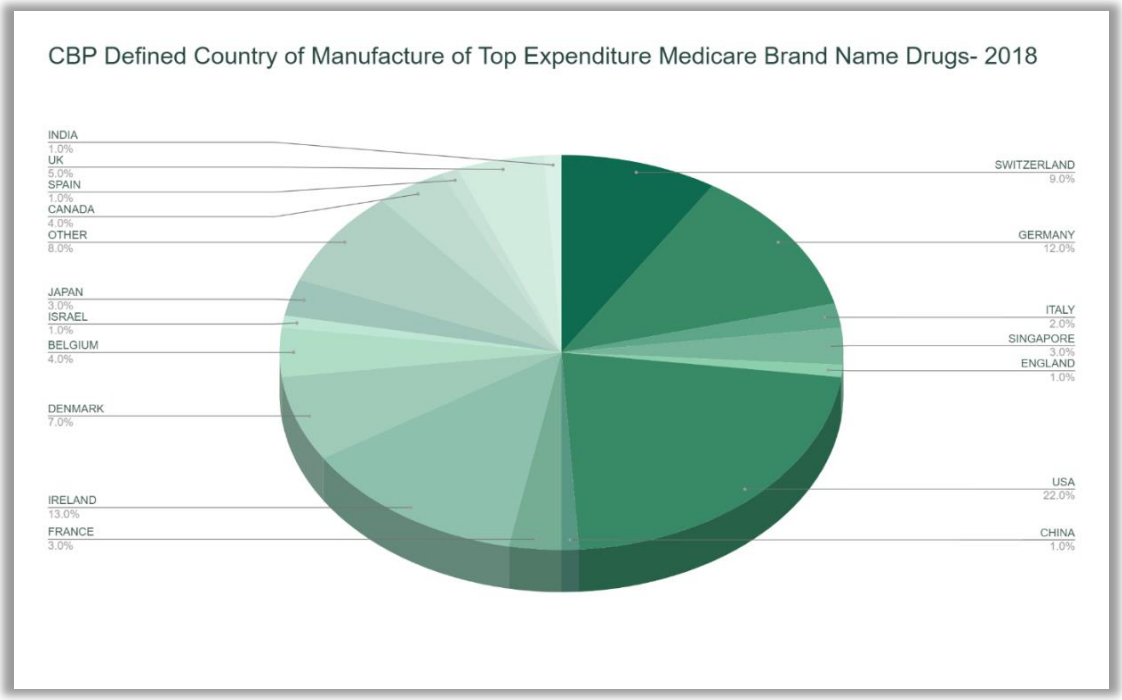
    - The Exceptions:

        - Neurontin (gabapentin). The label reads that it is “Made in India,” indicating that both the API and FDF are manufactured in India. Gabapentin is widely available in the U.S. as a generic.
        - Imbruvica (ibrutinib). The label reads “Active ingredient made in China.” A drug company representative said that “the manufacturing, testing, packaging [of Imbruvica] is done across
        - multiple locations in the USA. This indicates that the API is manufactured in China and the FDF, in the USA.



SOURCE: PHARMACYCHECKER RESEARCH, 2021

- Apart from Imbruvica, all countries of origin making brand name drugs from the dataset are democratic allies, indicating that national security vulnerability is less of an issue when it comes to brand name drugs.



SOURCE: PHARMACYCHECKER RESEARCH, 2021

2.4. 2021 U.S. vs. International Retail Brand Name Drug Prices

In addition to country of origin, "Not Made in the USA" researchers collected and compared U.S. and foreign retail drug prices of products in our dataset. We compared our data to the robust analysis into comparative international drug pricing from the Rand Corporation's 2021 report called "International Prescription Drug Price Comparisons: Current Empirical Estimates and Comparisons with Previous Studies."[40] Its focus was on *wholesale* prices. The data in "Not Made in the USA" on *retail* drug prices corresponded strongly with Rand's analysis.

Rand's top-level finding on brand name drug prices is that U.S. prices are 344% higher than the average of member countries of the Organisation for Economic Cooperation Development (OECD). Reversing the percentage into a discount, Rand found that prices are on average 71% lower outside the United States. For **the top 60 drugs** by sales in Rand's study, the difference is 394% higher in the U.S., meaning approximately 75% lower outside the United States. The respective finding in "Not Made in the USA" is 75.53%. For just pharmacies in Canada, Rand's findings show prices are 294% higher in the U.S., meaning 66% lower in Canada. The respective finding in "Not Made in the USA" is 70.18%.

The parallel findings, especially in view of the different methodologies, between the Rand report and this report on pricing, point to the accuracy of the data.

The price comparisons in Appendix A were collected in May 2021. The dataset for pricing is based on the top 100 brand name drugs by expenditure in Medicare in 2018 *that are available for sale* from foreign online pharmacies that ship medication internationally.[v]

- ❖ Top brand name drugs sold in U.S. pharmacies are 385% more expensive than international mail-order drugs.
- ❖ Top brand name drugs sold in U.S. pharmacies are 357% more expensive than available at *Canadian* mail-order drugs.

Section 3: Our Global Pharmaceutical Supply Chain

3.1. Data Overview of Pharmaceutical Imports

The finding in this report, that 78% of APIs for the dataset of 100 drugs are imported, appears to corroborate the FDA's ubiquitous datapoint of 80%, but this dataset consists *only of brand name drugs*. It is likely that an even higher percentage of generic drugs are imported. Public Citizen's Trade Watch data for 2019, on the volume and dollar values of the top 10 countries exporting pharmaceuticals to the U.S., supports that assertion.[41] The largest quantity of pharmaceutical imports is generic drugs and not from the most strongly regulated pharmaceutical

v Drug prices came from foreign online pharmacies that are PharmacyChecker-accredited, meaning online pharmacies that meet important safety criteria. Prices are taken from pharmacies that dispense drugs approved in Australia, Canada, India, Israel, New Zealand, Turkey, or the United Kingdom. Canadian pharmacy prices are those taken from pharmacies that only dispense medication in Canada.

markets. Notice that the top three countries for volume of pharmaceutical imports are 1) China, 2) India and 3) Mexico.

Top 10 U.S. Sources of Pharmaceutical Imports by Volume vs. Value of Those Imports (2019)

			Percent of Total	
Country	Kilograms	Dollar Value	Kilograms	Dollar Value
China	101,950,825	$1,614,171,438	22.46%	2.05%
India	97,847,782	$7,597,811,241	21.56%	9.65%
Mexico	85,409,777	$567,164,001	18.82%	0.72%
Canada	50,908,177	$5,307,652,313	11.22%	6.74%
Germany	32,067,235	$17,316,667,285	7.07%	22.00%
Italy	30,181,545	$7,718,831,907	6.65%	9.81%
United Kingdom	16,736,681	$5,101,369,001	3.69%	6.48%
Israel	13,529,322	$2,209,704,960	2.98%	2.81%
Spain	12,680,293	$1,323,775,643	2.79%	1.68%
Ireland	12,522,083	$29,941,109,004	2.76%	38.05%
Total	453,833,720	$78,698,256,793		

SOURCE: PUBLIC CITIZEN, 2019

In our dataset of 100, China and India each accounted for only one API.

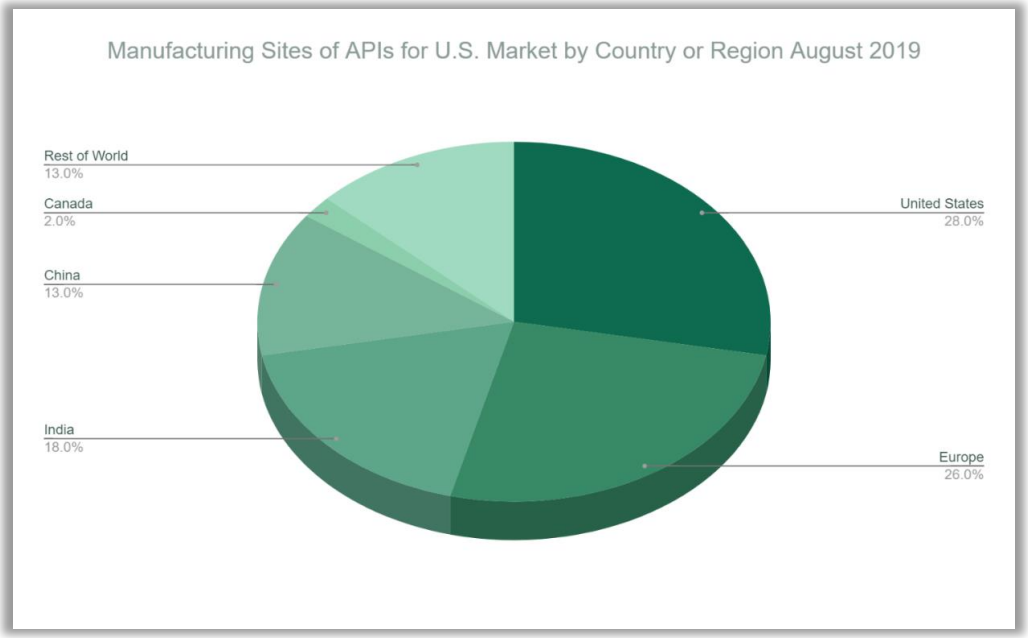
After the top three countries for pharmaceutical imports, the rest are high-income countries: 4) Canada, 5) Germany, 6) Italy, 7) the United Kingdom, 8) Israel, 9) Spain, 10) Ireland. In looking at the dollar value data, the bulk of imports from high-income countries must be brand name APIs and FDFs. Ireland, for example, makes up only 2.76% of the *volume* of the top 10, but a plurality, 38.05%, of the *dollar value*. That reflects the much higher cost of brand name vs. generic drugs. The inverse is true of China: its import volume is 22.46% of the top 10 countries, compared to only 2.05% of the dollar value. This data confirms that high-income countries with the strongest pharmaceutical regulations are mostly responsible for the manufacture of our brand name drugs. Further validating evidence is found in a survey conducted in 2018 showing biopharma industry perceptions of countries that lead in the manufacture of biologics in which the top countries identified are the U.S., Germany, Japan, Italy, the UK, and Ireland.[42]

Two salient truths that contradict the prevailing communications narrative of the FDA in both instances, and biopharmaceutical industry in just the latter, are identified and explained in this section of the paper:

- One, brand name drugs are likely to be of higher quality than generics. That is because branded finished products and their active pharmaceutical ingredient are mostly made in countries with the strongest regulations for pharmaceutical manufacturing.
- Two, as a corollary of the above, there is no reason to prevent importing of lower cost brand name drugs into the U.S. based on arguments over risks of lower drug quality.

3.2. FDA Registration and Recordkeeping About Foreign Made Drugs: APIs and FDFs

This section explores the FDA's statutory mandate for registering and recordkeeping of drug imports, clarifies what data they do and do not have, and what we should expect from the agency. As stated above, the GAO, relying on FDA data, asserted in 1998[43] and as recently as 2019, that 80% of APIs in U.S. drugs are foreign made.[44] The fact that this figure remained unchanged after 20 years would have us conclude that the globalization of pharmaceutical manufacturing happened long ago and is not necessarily increasing at all. It also indicates lack of FDA's data accuracy and highlights the GAO's failure to question that data.



SOURCE: FDA, 2019

In 2019, the FDA stated that not only does it not know the exact percentage of APIs that are imported but it *cannot know*.[45] In Congressional testimony for a hearing called "Safeguarding Pharmaceutical Supply Chains in a Global Economy," in October of 2019, then FDA Director of the Center for Drug Evaluation and Research (CDER), current acting FDA Commissioner Janet Woodcock, MD, stated:

> "…although CDER can describe the locations of API manufacturing facilities, we cannot determine with any precision the volume of API that China is actually producing, or the volume of APIs manufactured in China that is entering the U.S. market, either directly or indirectly by incorporation into finished dosages manufactured in China or other parts of the world."
>
> "… data available to FDA do not enable us to calculate the volume of APIs being used for U.S.-marketed drugs from China or India, and what percentage of U.S. drug consumption this represents."[46]

This registration data is helpful in assessing dependency on foreign drug supplies and as an overview of what countries and regions are key sources of APIs for the United States. FDA's data does show a growing number of

Chinese API producers registered with the FDA but also very strong European penetration in this market. FDA's data also shows that 72% of registered facilities are based outside the United States, which closely corroborates the pharmaceuticals import data in "Not Made in the USA."

With a total of 1,788 registered manufacturing establishments, the largest share after the U.S. is in Europe: 456 facilities. This data approximates the findings in "Not Made in the USA" and Public Citizen's analysis of U.S. trade data that both show a very prominent role played by European countries in supplying the U.S. with brand name drugs.

The statutory registration requirements for drug manufacturers under federal law do not require the FDA to track the volume of pharmaceutical imports but do require that the FDA keep records at the national drug code (NDC) level of where finished drugs and APIs are made:

> "Every person who registers with the Secretary under subsection (b), (c), (d), or (i) shall, at the time of registration under any such subsection, file with the Secretary a list of all drugs and a list of all devices...which are being manufactured, prepared, propagated, compounded, or processed by him for commercial distribution and which he has not included in any list of drugs or devices filed by him with the Secretary under this paragraph or paragraph (2) before such time of registration. Such list shall be prepared in such form and manner as the Secretary may prescribe and shall be accompanied by-"[47]

For foreign establishments specifically:

> "1) Every person who owns or operates any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or device that is imported or offered for import into the United States shall, through electronic means in accordance with the criteria of the Secretary- (A) upon first engaging in any such activity, immediately submit a registration to the Secretary that includes-…the name and place of business of such person, all such establishments, the unique facility identifier of each such establishment…"[48]

Based on those requirements, a database should exist in which the FDA can immediately refer to the name and location of the manufacturer for any given API or FDF. Drug manufacturers often work with several companies to supply them with the same API, which could possibly complicate mandated recordkeeping, but for FDFs it is more straightforward. Each FDF has an NDC number, which is associated with a drug application that must have the name and location of the manufacturer. Based on those requirements, the FDA drug database should be able to provide accurate information on the percentage of

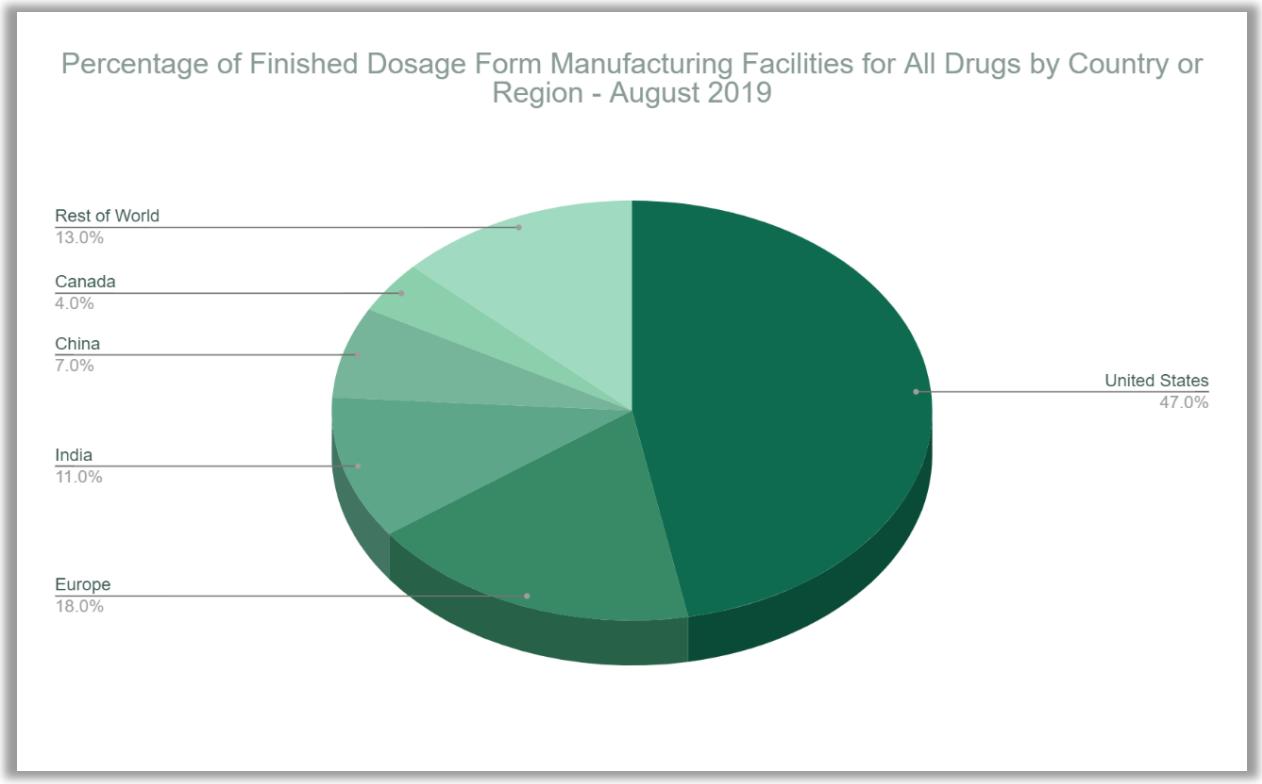
FDA-Registered Facilities

Program	Domestic	Foreign	Total
Animal Drugs	1,608	1,156	2,764
Animal Food	40,826	25,023	65,849
Biologics	5,112	467	5,579
Human Drugs	3,568	3,970	7,538
Human Food	90,646	131,844	222,490
Medical Devices	13,010	12,854	25,864
Tobacco	3,067	0	3,067
Total	**157,837**	**175,314**	**333,151**

SOURCE: FDA, 2020

available drugs — but not the volume — that are imported, at least under the FDA's definition (contrasted with the definition of the CBP). If any such report or recordkeeping exists, it is not referenced by the FDA as the basis for its claims about the percentage of the U.S. drug supply that is imported.

Where the FDA falls short on recordkeeping or transparency about imported drugs, it has improved its procedures for registering and updating drug establishments that manufacture drugs for the U.S. market, a product of the Food and Drug Administration Safety and Improvement Act of 2012.[49] An FDA Fact Sheet from



SOURCE: FDA, 2019

November 2020 shows that there are a total of 7,538 registered human drug establishments, many of which do not actually produce drugs but re-package and re-label them.[50] It states that "(a)bout 80 percent of active pharmaceutical ingredient manufacturers are located outside of the U.S." Notice that the statistic is about foreign API manufacturers, not API import volumes or products. In other testimony before Congress, in December 2019, Dr. Woodcock submitted a breakdown of establishments registered with the FDA for making FDFs, which contains a surprisingly high percentage — 47% — located in the United States.[51]

That figure does not square with the percentage of FDFs *sold* in the U.S. that are produced domestically. The reason is that many such establishments are *labelers* and *packagers* — not *manufacturers*.

3.3. Brand vs. Generic Drug Supply Quality Concerns

3.3.1. Foreign Generic Drug Manufacturing Quality

The public perception is that there are more quality problems with generic drugs than brand name drugs.[52] Drug testing demonstrates that this perception is based on the reality that a significant number of generic drugs are

not interchangeable with their brand name counterparts or with other generic counterparts (different manufacturers of the same drug) due to quality problems.[53] [54] This is not a reason to fearmonger about or discourage use of generic drugs. **Most generic drugs in the U.S., in high-income countries generally, and those of the top manufacturers in India as well, are generally of high quality and are the foundation for drug accessibility and affordability in the U.S. and globally**.[55] [56] [57]However, ignoring the fact that generic drugs are more likely to have quality control problems and that brand name drugs are generally made in countries with the strongest pharmaceutical regulations will hinder our ability to make the best public health and healthcare financing decisions.

Over the past two decades, periodic GAO reports have criticized the FDA for not adequately inspecting foreign drug manufacturing establishments that export pharmaceuticals to the United States.[58] [59] [60] [61] Subpar inspections of API manufacturing facilities, located in countries with weaker pharmaceutical regulations, are usually discussed as a growing problem that is overwhelmingly associated with India and China, the world's largest producers of pharmaceutical ingredients. As recently as March 2021, the GAO released a report documenting a lack of confidence in FDA inspection activities during the COVID-19 pandemic:

> "We have long-standing concerns about the Food and Drug Administration's ability to oversee the increasingly global pharmaceutical supply chain."[62]

The ubiquitous criticism of the agency notwithstanding, the FDA, as noted above, has improved its protocols for inspecting and registering foreign drug establishments, but its ability to inspect was hampered by the pandemic.

India is a longtime, major supplier of generic drugs, FDFs and APIs, to the United States. A *Chemistry and Engineering News* article summarizes the trend of U.S.-sold generics imported from India:

> "In 1990, about 50% of ANDAs [abbreviated new drug applications (generics)] came from U.S. firms and 15%, from India. By 2012, U.S. company filings had dropped to 30% and Indian ones had grown to 40%."[63]

In a CNBC article from March 24, 2020, Rohit Bhat, research analyst at B&K Securities, estimated that India accounts for 40-50% of all generic drugs.[64] Also, according to that article, India imports 70% of its APIs from China for its own drug supply. It is not documented how many of those APIs are used to manufacture FDA-approved drugs formulated in India; this is an opaque aspect of the supply chain where tallying Chinese-made APIs in U.S. drugs is difficult.[65]

Drug manufacturing problems and regulatory non-compliance happen in the U.S. and in other high-income countries, but not to the degree found in India and China.[66] Both India and China have state-of-the-art pharmaceutical manufacturing capacities that produce drugs of the highest quality — but also many lower-quality producers.[67] "Bottle of Lies: The Inside Story of the Generic Drug Boom," by investigative journalist Katherine Eban, uncovered numerous cases of corruption and incompetence by drug manufacturers in India. The book presents a scathing view of the FDA, accusing the agency of turning a blind eye to this corruption and alleging that the "generic drug boom" of the past two decades has gone hand in hand with poor regulatory oversight.[68] The authors of "Not Made in the USA" hold a less critical perspective, but Ms. Eban's important reporting corroborates the position taken here that brand name drugs are sometimes of higher quality than

generics: because they are far more likely to be produced in countries with the strongest pharmaceutical regulations.

3.3.2. Regulatory Equivalence Or Superiority in Other High-Income Countries

"Not Made in the USA" data shows that brand name drugs are mostly made outside the U.S. in high-income countries with strong regulatory standards and oversight bodies. The FDA officially recognizes the strong pharmaceutical regulations of these trading partners. As of 2019, the FDA had entered into mutual recognition agreements (MRAs) with all 28 (now 27) member countries of the European Union that allow the FDA to recognize the results of foreign drug manufacturing facility inspections for Good Manufacturing Practices (GMPs) by one of the MRA countries.[69] [vi]

The FDA's decision to rely on the regulators of other countries is supported by research conducted by the agency's leadership showing the superiority of foreign regulators, particularly those in the EU. That research led the U.S. Department of Health and Human Services to see the benefits of personal drug importation for patients to save money. In a question-and-answer page offered on the HHS website, it stated, "Can individuals trust that imported prescription drugs are safe?"[70]:

> "A recent report based on the largest ever comparative test of the quality attributes of prescription drugs legally marketed in the United States concluded that 'difficult-to-make prescription pharmaceuticals marketed in the US consistently meet quality standards even when manufactured outside the US.'"[71]

The report found that manufacturing facilities in the EU had the strongest outcomes for compliance, noticeably superior to U.S.-based facilities. While drug manufacturing facilities in the U.S. had better outcomes than those in China and India, they were slightly worse than other countries generally. [72] Furthermore, quality testing results for brand

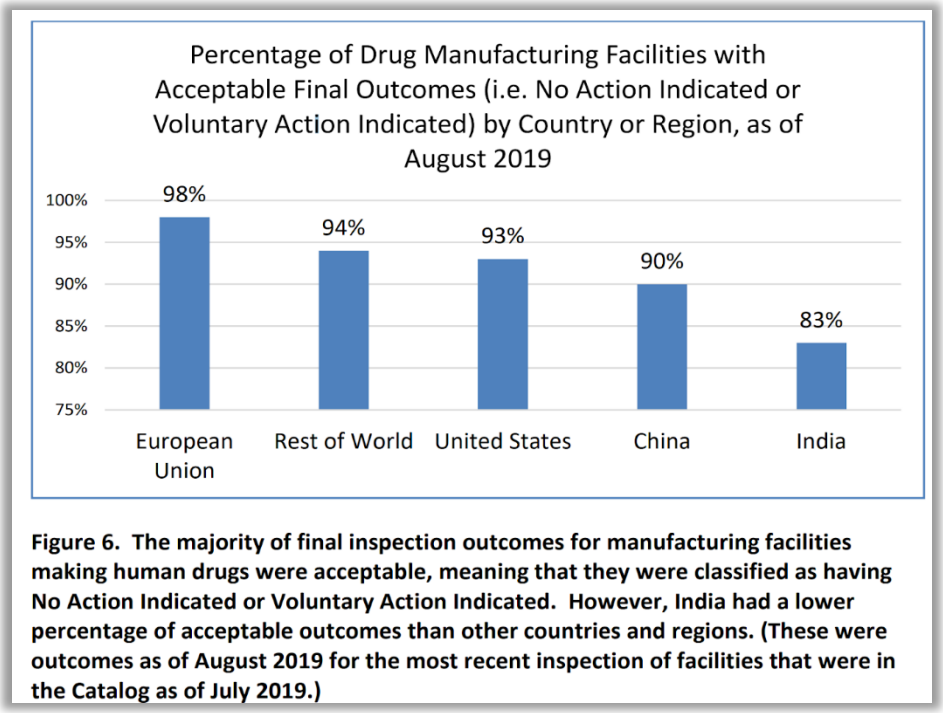


Figure 6. The majority of final inspection outcomes for manufacturing facilities making human drugs were acceptable, meaning that they were classified as having No Action Indicated or Voluntary Action Indicated. However, India had a lower percentage of acceptable outcomes than other countries and regions. (These were outcomes as of August 2019 for the most recent inspection of facilities that were in the Catalog as of July 2019.)

SOURCE: FDA, 2019

vi Furthermore, the European Union, which has led global regulatory cooperation on pharmaceutical manufacturing, also has MRAs with Australia, Canada, Israel, Japan, New Zealand, and Switzerland. See: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra#canada-section.

name drugs were notably stronger than those for generic drugs. The report stated, "all drugs met the tested standards, brand-name drugs generally had higher process performance for dissolution [than generic drugs]."[73]

It bears repeating that the greater degree of quality control with brand name drugs is not to diminish the importance and necessity of generic drugs for managing the cost of and access to pharmaceuticals. **Properly manufactured generics, meaning those made with high quality ingredients and under GMP, work just as well as their brand name counterparts.** Valisure, an online pharmacy and independent drug testing laboratory in the U.S., finds that 90% of generic drugs they test meet quality standards.[74] Those tests surpass the FDA's protocols for ensuring drug quality.[75] In an overwhelming majority of cases, FDA-approved generics work just as well as the brand. The problem is that a 10% failure rate is too high.

3.3.3. National Security

As regulators and policymakers continue to examine potential vulnerabilities of the U.S. pharmaceutical supply, concerns are often placed on imports from China and, to a different degree, India. In view of the global coronavirus pandemic, quality and accessibility of pharmaceuticals are viewed with greater urgency.[76] In March 2021, President Biden issued an executive order requiring review of critical supply chains with a stated aim to boost domestic manufacturing of pharmaceuticals.[77]

In the case of China, pharmaceutical supply chains are a source of vulnerability, the degree to which is an important topic for policymakers. However, "Not Made in the USA" shows that such vulnerabilities may not apply to the manufacture of brand name drugs. While China is the largest supplier of pharmaceutical ingredients to the U.S., only one drug in our sample of 100 drugs was made with an API from China.

The FDA has identified APIs and pharmaceuticals that demonstrate the level of U.S. dependence on China.[78] To counter those vulnerabilities, public policies that develop and ensure adequate domestic or alternative global pharmaceutical manufacturing capacity are necessary. Thus, in addition to building more domestic manufacturing capacity, the FDA's data and this report show alternative global manufacturing bases beyond China, notably in the EU and India, that can be tapped in emergencies.

Exaggerations about the U.S. drug supply's vulnerability can lead to bad policy and public health consequences, due to a lack of trust in the efficacy of prescription drugs and even higher drug prices that would result from more protectionist trade policies. To protect and improve drug safety, getting the data right is critical before embarking on dramatic regulatory reforms. Reasonable efforts to build more domestic manufacturing capacity need not trample on a more efficient and safer global marketplace for pharmaceuticals.

Section 4. Importation as Policy to Lower Prescription Drug Prices

The U.S. drug supply chain relies on pharmaceuticals produced in other countries and drugs are priced much lower in those foreign countries. For years, federal law has unnecessarily protected drug companies by preventing commercial or wholesale pharmaceutical trading that would lower drug prices here. Recent developments have opened the door to end that protectionism. Policymakers and businesses interested in drug importation can make use of "Not Made in the USA" data to identify products for wholesale or personal

importation permissible under current law. Legislative reforms, however, are still necessary to use importation to more substantially lower drug prices for Americans.

The pharmaceutical and the U.S. pharmacy industries oppose new drug importation pathways as a means to make lower drug prices available to Americans.[79] [80] Those industries would generate lower profits if public policies encouraged and led to substantially greater drug importation.[81] The industry's public opposition focuses on the potential for importing lower quality or counterfeit drugs from countries with weak regulations[82] and funding organizations to exaggerate the threats.[83] [84] [85] [86] [87] [88] "Not Made in the USA" shows the hollowness of the industry's opposition, especially when it comes to importing lower-priced brand name prescription drugs from high-income countries.

Section 4 explores four drug importation pathways to lower drug prices in the United States. The fifth and final subsection lists practical policy recommendations for the federal government given the findings in "Not Made in the USA."

4.1. Wholesale ("Commercial") Drug Importation

4.1.1. History and Limitations of Current Law

In 2000, the Medicines Equity and Drug Safety Act (the "MEDS Act") created Section 804 of the FDCA to allow, as a means to lower drug prices for American payers, wholesale drug importation from 25 countries: Australia, Canada, Israel, Japan, New Zealand, Switzerland, or South Africa; and countries of the European Union (18 member states at the time).[89] The "poison pill" in the law was that, in order for it to come into effect, it was required that the Secretary of the Department of Health and Human Services certify that the proposed importation: (1) pose no additional risk to the public's health and safety; and (2) result in a significant reduction in the cost of covered products to the American consumer.[90] Essentially, if those certifications had been made, Section 804 would have integrated the United States with the EU and other countries in a system of free trade in pharmaceuticals at the wholesale level with accompanying beneficial competitive price effects: lower drug prices in America.

In 2003, the Medicare Prescription Drug, Improvement, and Modernization Act amended Section 804 to only permit wholesale drug importation from Canada, but it added important and expansive provisions to allow personal drug importation based on "enforcement discretion," waivers, or regulatory guidelines.[91] This revision contained the same certification requirements as the MEDS Act. However, as discussed below, it set a different, more permissive standard for personal drug importation.

The certification called for under Section 804 by the HHS Secretary is one upon which the FDA, an agency under HHS's authority, would play a lead role. For two decades now, the FDA's intransigence and pharmaceutical industry lobbying of the FDA, explains why, until 2020, no HHS Secretary made the certification.

The status quo on drug importation and Section 804 was upended under the Trump administration. An executive order was issued on Jul 24th, 2020, calling for certification and the finalizing of the rules to implement Section 804; waiver authorities, creating new permissions of personal drug importation; and reimportation of insulin pursuant to Section 801 of the FDCA.[92] Under the Trump administration, on September 23rd, 2020, the Section 804 certification was officially made by HHS Secretary Alex Azar.[93] Thus, pursuant to Section 804 of the

FDCA, and new federal implementing rules, it is legal for entities other than drug manufacturers to import and resell lower cost prescription drugs from Canada.[94] While the Biden Administration revoked other executive orders on drug prices issued under the Trump administration, the one supporting importation remains.

On November 23rd, 2020, the Pharmaceutical Researchers and Manufacturers of America (PhRMA), the Partnership for Safe Medicines, and the Council for Affordable Health Coverage filed a lawsuit to overturn HHS's Section 804 certification and the final rule.[95] The Biden administration, while signaling that wholesale importation from Canada under Section 804 may not happen soon, defended the certification and final rule of Section 804 in a motion to dismiss PhRMA's lawsuit.[96]

4.1.2. State Importation Programs and Section 804

Section 804 makes wholesale importation of prescription drugs from Canada legal by entities other than the manufacturers of those drugs, subject to implementing protocols to ensure the safety of the process.[97] Those protocols include mandated reporting on drugs intended for import, batch testing for quality, and registration of Canadian wholesale pharmacies.[98] Before wholesale importation can commence under Section 804, Section 804 sponsors must present their programs to the HHS Secretary for approval under the new rule. Thus, administrative obstacles remain as it relates to new wholesale Canadian drug importation programs.[99]

With prescription drug costs becoming a larger share of state budgets, among other policies to tackle drug prices, several U.S. states have passed laws to encourage wholesale importation from Canada, subject to Section 804 rules. In 2017, the National Academy for State Health Policy (NASHP), as part of its project to help lower the cost of prescription drugs, published model state legislation for the importation of drugs from Canada.[vii] [100] [101] Six states have passed drug importation laws that to varying degrees rely on the NASHP model legislation. Under the final rule, to implement Section 804, states are required to submit to their importation program plans to HHS for approval before importing.[102] Several states have submitted their Section 804 plans to HHS, but none are approved.

Importation from Canada under Section 804 may provide some prescription savings for states and their residents, but the programs have important limitations and face obstacles to advancement. Notably, the law excludes importation of biologics, the most expensive medical products and the ones that account for an increasing percentage of spending on pharmaceuticals.[103] [104] It also excludes controlled drugs, such as prescription opioids, benzodiazepines, and amphetamine-based medicines, intravenous and inhaled drugs. [105]

Moreover, the federal rule only allows drugs to be imported from Canadian wholesalers that received those drugs directly from manufacturers, a restriction not required under Section 804.[106] This requirement will weaken the competitive benefits of importation by making it easy for drug manufacturers to limit supplies to those Canadian wholesalers that are exporting products to the United States. That concern is well founded because the pharmaceutical industry has a history of instituting supply restrictions on Canadian pharmacies that sell prescription drugs to U.S. consumers for personal import.[107] Large pharmaceutical companies have software to accurately predict the number of pharmaceuticals that an economically advanced country uses for its own

vii The main author of the model state drug importation bill is public policy analyst Jane Horvath.

population. They will not likely cooperate by increasing the number of drug supplies for Canadian wholesalers to export to the United States. This part of the new rule undermines the price competitive benefits of importation by helping pharmaceutical companies maintain their distribution monopolies.

As the U.S. has determined that the importation of prescription drugs approved for sale in Canada poses no additional risk to the public health, there is no need to create a distribution bottleneck that empowers drug manufacturers. Another reason it is unnecessary to require that imported drugs come from a Canadian wholesaler that received them directly from their manufacturers is that Section 804 requires independent batch testing, beyond the requirements mandated for importation by drug manufacturers. In effect, due to enhanced testing, the Section 804 drug imports have potentially greater safety profiles than other drugs sold in the United States.[108]

Perhaps the most difficult obstacle has become the Canadian government's position that the new Section 804 importation pathway is a potential threat to maintaining adequate drug supplies for Canada (which has a population about 12% the size of the United States).[109] Fearing potential shortages, Canada issued an interim order in response to Section 804 requiring Canadian wholesale pharmacies to demonstrate, prior to export, that exports will not create domestic shortages.[110] Eligible wholesale pharmacies in Canada would need to increase their orders from manufacturers to meet U.S. demands, while not jeopardizing local Canadian supplies.

Overall, the Section 804 importation pathway from Canada has limited long-term impact because the Canadian market's small size threatens to restrict the American supply.[111] However, the drawbacks mentioned are not insurmountable to *achieve substantial savings on some patented and off-patent expensive non-biologic drugs*. Some of the drugs mentioned in this report are candidates for savings.

In the longer term, the operationalization of Section 804 marks the beginning of the process to end U.S. trade protectionism in pharmaceuticals. Recently introduced legislation at the federal and state levels have called for the expansion beyond Canada of permissible wholesale importation from other high-income countries, such as those included in the MEDS Act.[112] [113]

4.1.3. Section 801 and Multi-market Approved Drugs

Confusing as it may seem, the FDA has issued guidance, pursuant to Section 801 of the FDCA, for drug manufacturers to import and sell FDA-approved drugs — ones initially planned for sale in another country — at lower prices.[114] In the FDA's guidance, these are called multi-market approved (MMA) products.[115] In drug manufacturing establishments in Europe, drugs are labeled for domestic European markets, not for the United States. Many of those drugs, apart from the labeling, are FDA-approved drugs and eligible under this pathway. There is no country limitation placed on manufacturers who import drugs into the United States.

Why would the same drug companies that already import many of their drugs, charging higher prices to American compared to Canadian or European wholesalers, lower their prices? According to the FDA's guidance, drug manufacturers have told FDA personnel that they are sometimes locked into higher prices:

> "Recently, FDA has become aware that some drug manufacturers may be interested in offering certain of their drugs at lower costs and that obtaining additional NDCs for these drugs may help them to address certain challenges in the private market."[116]

This new guidance appears to call the bluff of drug companies: it allows them to circumvent contracts more easily with third parties by creating new NDCs for the exact same drugs that were intended for sale outside the U.S. Those "challenges in the private market" pertain to drug price discount and rebate negotiations with private third parties, such as pharmacy benefit managers and other payers. All drugs have an NDC, and, attached to each NDC, a list price. By creating a new NDC for MMA drugs, manufacturers could lower the prices because the new NDC would not be part of any existing third-party discount or rebate contracts.

At the time of this writing, drug manufacturers have not brought a product to the US market using this new importation pathway.

This pathway, however, raises important questions about how many currently FDA-approved drugs could qualify as MMA products.

Many of the drugs assessed in "Not Made in the USA" fall into the category of MMA products. Some of the U.S.-sold drugs identified under FDA's definition as "imported" are ones sold in other countries as well. If the manufacturers could make the same profits cutting out middlemen with lower prices in the U.S., then it is conceivable that this guidance will be used, but it will be done sparingly so and without great effect.

4.2. Allowing Personal Drug Importation

Unlike the importation pathways mentioned above, personal importation already benefits Americans.[117] Safe personal drug importation occurs through programs offered in numerous self-insured U.S. municipalities, labor unions, and other organizations; patient assistance services, often referred to as "pharmacy storefronts," offices where people get help to buy a lower cost drug from Canada and other countries; and properly credential international online pharmacies.[118] Vastly lower drug prices in other countries explain why, according to a Kaiser Family Foundation survey, an estimated 20 million people in the U.S. had imported prescription drugs by 2016, a number that is likely higher.[119] As the survey authors point out, it's possible that some respondents didn't want to go on record about their medicine purchases or having done something that may have been technically illegal.[120] Also, it does not account for older Americans who were importing prescription drugs before the advent of the Medicare Part D program and who had died by the time of the survey.

Lower-priced drugs are purchased in person by traveling to another country, or via mail order, often using online pharmacies.[121] Uniquely, personal drug importation can be permitted but, under most circumstances, is illegal under U.S. law.[viii] The reality that tens of millions of individuals importing prescription drugs for their own use have never been prosecuted — or even charged — shows that the practice is effectively, or *de facto*, decriminalized.

A more accurate figure of how many people have imported a prescription drug for personal use is probably about 40 million over the past 20 years. That estimate extrapolates from a 2019 analysis in the Journal of the

viii In Section 804 of the Food, Drug and Cosmetic Act, Congress "declares" that the Secretary of Health and Human Services, which administratively would devolve to the FDA commissioner, "should" permit otherwise prohibited drug importation as long as the importers are individuals obtaining prescription drugs for their own use that are not an "unreasonable risk."

American Medical Association (JAMA) showing that 2.3 million people *with a prescription* for that medication personally imported a prescription drug because of cost.[122] That number does not account for people importing drugs each year who do *not have a prescription, a practice that should be discouraged*.

One example of a personal drug importation program authorized by a state government was launched by the Utah Public Employees Health Program in 2019. The state pays eligible employees to travel to Mexico to obtain prescription drugs at much lower cost.[123] It is limited to very expensive drugs that most affect the state's budget.[124] In 2020, about 10 state employees were given money for flights to Mexico, a $500 per trip bonus, and Utah's government saved tens of thousands of dollars in medication costs.[125]

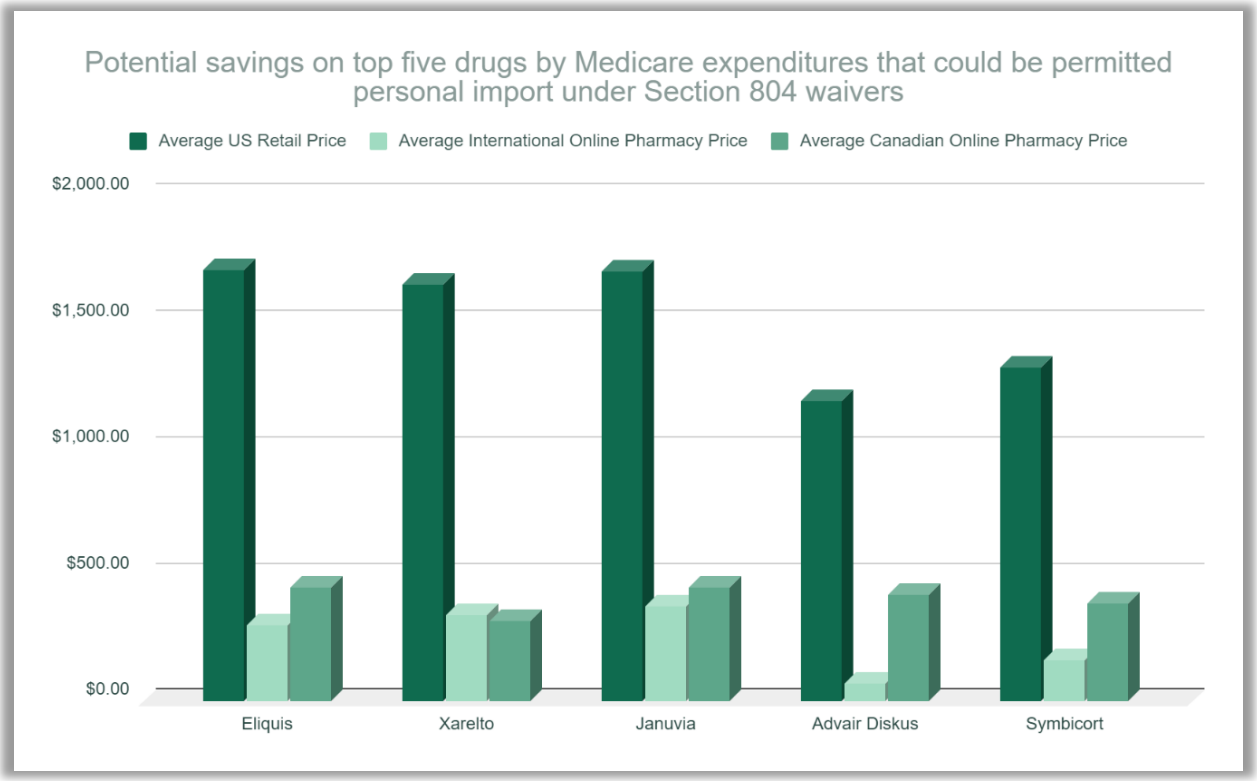
Personal importation occurs despite the fact that the FDA has issued a largely blanket public warning against personal imports of lower cost drugs, even from Canada and other high-income countries.[126] The FDA's enforcement regime for personal drug importation can be metaphorically described as a yellow traffic light for pedestrians. The agency's position, therefore, does not fully explain why only about 1.5% of Americans avail themselves each year of lower cost medicines from other countries. A huge deterrent is the false or misleading public information campaigns funded by pharmaceutical companies that warn people against it.[127] In the absence of those warnings, a far greater number of Americans would import prescription drugs, creating downward pricing pressures in the U.S. pharmaceutical market.[128]

While it has the statutory mandate to do so, the FDA does not regularly "allow" personal importation of prescription drugs to help Americans obtain lower prices.[129] However, the FDA sometimes refuses and destroys international prescription drug orders.[130] Personally imported medicine often comes into the country via international mail facilities, where U.S. Customs and Border Protection screen packages.[131] Over the past three years, due to greater congressional appropriations to curb opioid imports at international mail facilities, it appears that more Americans are seeing their prescription orders taken away.[132]

Since it is no longer tenable to question the relative safety of drugs in Canada or Europe compared to the U.S., opponents of personal importation rely on threats surrounding the dangers from the Internet and the assumed inability of a consumer to find a licensed pharmacy outside the U.S. from which to purchase a more affordable prescription drug.[133] PharmacyChecker.com plays a critical, private sector verification role in this respect by accrediting online pharmacies that process orders internationally filled by licensed pharmacies that require legitimate prescriptions.[134] Additionally, members of the Canadian International Pharmacy Association (CIPA) are recognized for providing safe international pharmacy services.[135] A public sector or non-profit initiative to provide those verification and information services, such as one led by the FDA, could help many more Americans benefit from safe personal drug importation.

4.2.1. Executive Orders on Personal Drug Importation

On July 24, 2020, the Trump Administration's Executive Order on drug importation called for expressly permitting personal drug imports.[136] Under this EO, the FDA could assume an official role in identifying licensed pharmacies, including online pharmacies, and permit American consumers to order from them.



SOURCE: PHARMACYCHECKER RESEARCH, 2021

EOs on drug prices under the Trump administration were generally criticized for having political motivations and little potential for implementation or impact.[137] The EO on personal drug importation does not fall into the *latter* category. As stated above, millions of Americans have already realized savings from personal drug importation; for many of them, it has meant taking a prescribed drug that they could not otherwise afford.[138] Yet due to the federal restrictions and misinformation about the dangers of "foreign drugs," the reach of personal drug importation has been limited.[ix] [139] With the executive order still on the books under the Biden administration, the scope of its impact depends largely on the willingness of HHS to expand its use.

Based on the EO, HHS issued two requests for proposal (RFP) on September 24, 2020, calling on interested parties to formulate and submit for review new programs for safe personal drug importation.[140] [141] One RFP on personal importation proposes that American consumers apply to HHS for individual waivers to obtain express permission to import.[142] One requirement of the RFP is that the imported drugs would have to be dispensed from a licensed U.S. pharmacy, instead of directly from a licensed foreign pharmacy, limiting the potential benefits by creating a middleman. One of the comparative advantages of personal drug importation, compared to wholesale drug importation, is that there is no middleman to cut into potential savings.

ix Roger Bate writes: "A debate about how to provide cheaper drugs for these Americans while protecting US businesses is entirely legitimate. But it is a debate that the industry does not think it can win. Instead of engaging in serious discussion, pharma companies and myriad industry-funded groups have scared Americans into believing that drugs from overseas pharmacies are inherently dangerous."

Highly supportive of the conclusions found in "Not Made in the USA" on safety is the RFP's list of countries from which personal importation would be permitted:

> "Under this pathway, individuals in the United States who have obtained waivers from the Secretary would be able to import certain FDA-approved prescription drugs from Australia, Canada, the European Union or a country in the European Economic Area, Israel, Japan, New Zealand, Switzerland, South Africa, or the United Kingdom (each an 'Acceptable Foreign Source')."

As "Not Made in the USA" shows, these are the countries in which the majority of expensive brand name drugs are manufactured. The key to the safety of personal importation is to ensure that the consumer is able to identify a licensed pharmacy in another country that requires a valid prescription and sells the same prescription drug they need at a much lower cost.[143]

The other RFP on personal importation called on HHS to create a pathway for the reimportation of insulin.[144] This request was launched based on a declaration by the HHS Secretary that, due to high domestic insulin prices, imports were "required for emergency medical care."[145] That declaration was made under Section 801(d)(2) of the FDCA, the statute that prevents drug imports for commercial use (re-sale), except by the drug manufacturers or due to an emergency. This policy concept was curiously narrow to only include reimported insulin: insulin made in the U.S. and exported for sale in another country. Of the three main and difficult to afford insulin products sold in U.S. pharmacies, Lantus Solostar (Sanofi Aventis), Humalog (Eli Lilly), and Levemir (Novo Nordisk), only Humalog is made in the U.S.

4.2.2. RFPs Withdrawn but HHS is Open to New Ideas on Personal Drug Importation

In July of 2021, HHS withdrew the RFPs on personal drug importation but is considering alternative personal drug importation programs.[146] By identifying the most efficient and safest channels for personal drug importation, federal and state governments, as well as non-profit and healthcare organizations, can greatly benefit patients who are unable or struggling to afford prescription drugs due to lack or inadequacy of health insurance.

"Not Made in the USA" data can help those who are working on drug importation programs, whether at the wholesale or personal importation level, by identifying the most expensive drugs and their countries of manufacture, along with the demonstrably substantial price discrepancies. The data in "Not Made in the USA" shows the degree to which the U.S. already relies on importation from the high-income countries identified. Creating FDA-approved pathways for personal imports from the countries identified in the RFP should be a priority.

4.3. Full, Open and Safe Parallel Trade in Pharmaceuticals Among High Income Countries

While new policy developments and federal rules have opened doors to importation programs that can help Americans obtain lower-cost drugs, the best path forward is for the federal government to expansively open trade in pharmaceuticals with high-income countries that have equally strong safety regulations to those of the United States.

Canada is too small and will not permit largescale, wholesale importation. Personal drug importation is of great value for individual consumers slipping through the healthcare system cracks. However, if that pathway is greatly expanded, it begs the question why we would not allow it at the wholesale level.

The European Union has open trade, referred to as *parallel trade*, in pharmaceuticals among member countries, despite opposition from drug manufacturers.[147] Economic analyses show that allowing parallel importation in the U.S. — from high-income countries, including wholesale and personal prescription drug imports— would substantially lower *domestic* drug prices.[148] Parallel trade is a market-based response to the monopolistic pricing effects of patents, and the differential ability of select markets to pay (e.g., less in Spain or Greece, more in France or Germany). According to its proponents:

> "...parallel imports are the only form of price competition during the period of patent protection of a medicine (called intra-brand competition). In other words, parallel trade in medicines creates competition in a business where patents provide the rights owner with a monopoly in every national market. This is good for the European economy, good for health care systems and good for patients."[149]

A successful model exists for this expansion. Strict regulatory protocols are in place for the safe distribution of pharmaceuticals throughout the European Union.[150] U.S. regulatory reforms to allow for safe parallel importation would require a substantial effort led by the FDA with commensurate costs, but the costs would be minimal compared to the overall savings by government payors and patients over time.

As previously mentioned, safety arguments about drug quality against parallel trade in brand name drugs ring hollow. "Not Made in the USA" shows a majority of the expensive brand name drugs we use are made in the EU and other high-income countries. They also manufacture many generic drugs. The U.S. now has memorandums of understanding (MOUs) with all European Union member countries in which their respective drug regulatory authorities are viewed as equal in ability to enforce standards for the safe manufacture of high-quality prescription drugs. During the Covid-19 pandemic, the FDA has accepted more such third-party arrangements substituting for in person, foreign inspections.[151]

The extent to which our drug supply already relies on importation is enough to warrant the reforms necessary to allow businesses other than drug manufacturers the ability to import drugs at lower prices from countries beyond Canada, specifically from the European Union. Thus, creating a regulatory framework for parallel trade in pharmaceuticals is the task at hand.

4.3.1. The Drug Supply Chain Security Act (DSCSA) is Not an Excuse Against Parallel Importation

Since the passage of the Drug Quality and Safety Act of 2013 (DQSA), the U.S. has embarked on and is far along in the process of mandating electronic track and trace systems for FDA-approved products from manufacturer to wholesaler, to pharmacy.[152] The goal is to "enhance FDA's ability to help protect patients from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful."[153] One of the central arguments made by respected opponents of drug importation under Section 804 is that it is not compatible with the Drug Supply Chain Security Act (DSCSA), Title II of the DQSA.[154] Yet even those arguments seem to simply give cover to the drug companies' drive to prevent "diversion," legal or illegal. The pharmaceutical industry believes that legal parallel trade in the EU is a form of drug "diversion."[155] Not surprisingly, in the DSCSA, an "illegitimate" drug is

one that is "is counterfeit, diverted, or stolen."[156] Thus, in some respect, the purpose of the DSCSA is to help drug manufacturers control their distribution channels to maximize profits.

The main argument against importation today focuses on the DSCSA-required serialization of a drug's package. Two noted industry experts, Adam J. Fein and Dirk Rodgers, write:

> "Products sold for the Canadian market lack a DSCSA-compliant standardized numerical identifier. This would irreparably break the necessary DSCSA tracking history, making the products permanently unsellable in the U.S."

There is a circular logic behind those statements, which can confuse policymakers and the public. Fein and Rodgers are saying that if the Health Canada-approved drugs do not have DSCSA identifiers, then they are unsellable in the U.S. *because the DSCSA makes it so*. True, but what does that have to do with the safety of those drugs? Drugs sold in Canadian pharmacies don't have DSCSA identifiers, but that does not make those drugs any less safe and effective than ones sold in U.S. pharmacies. For example, the drug Januvia (sitagliptin), made in the UK and Italy, is sold in Canada and the United States. The exact same Januvia is labeled differently for each market. Even well-regarded opponents of importation, such as former FDA commissioner Scott Gottlieb, MD, concede that the safety of the actual drug products in Canada is not in any doubt.[157] It is the distribution that scares many importation opponents. Supporters of importation contend that the DSCSA already accommodates prescription drug importation because many foreign factories making drugs for the U.S. market, the ones analyzed in this report, must be DSCSA-compliant.[158] This discussion about whether importation proposals now on the table can comply with the DSCSA detracts from the real issue, which is *whether the DSCSA should be updated to allow for parallel drug importation*.

If the answer is yes, then we should turn our attention to the European Union, which has its own version of track and trace that is arguably superior to the DSCSA.[159] Created under the EU Falsified Medicines Directive, all prescription drugs sold in the EU are traceable back to the manufacturers and scanned at the unit level, before dispensing to the patient.[160] The DSCSA lacks this scanning requirement and does not track at the unit level, which leaves products containing larger wholesale quantities vulnerable to tampering and adulteration, a problem of which the FDA is well aware.[161] Furthermore, implementation of DSCSA to date has not prevented counterfeit drugs from entering the "legitimate" supply chain, as evidenced by a major breach earlier this year where fake versions of Gilead's HIV drugs, Biktarvy and Descovy, reached U.S. pharmacy shelves.[162] That breach did not occur in the EU.

The U.S. already recognizes the safety of drugs made in the EU. We must also recognize that the EU's system of parallel trade in pharmaceuticals is vigorously regulated for safety. There is an honest debate about how to integrate new pathways for drug importation as a means to lower prices that will maintain safe distribution channels. In contrast, it is dishonest to assert that it cannot be done.

4.4. End the FDA's Trade Protectionist Regulatory Regime

The FDA is a global pioneer and leader among drug regulatory authorities, but it can no longer be viewed as superior to all other drug regulatory authorities in terms of its oversight role of drug manufacturing, safety, and quality. That pedestal is promoted by the pharmaceutical industry, which needs to maintain the public

perception of FDA's superiority to prevent price competition from parallel trade. In its myriad efforts to oppose drug importation legislation, for decades, the industry has pushed the narrative of the FDA as the "gold standard." A page on the website of the Pharmaceutical Researchers and Manufacturers of America called "The Dangers of Drug Importation" states:

> "The U.S. Food and Drug Administration (FDA) is the gold standard when it comes to regulating the safety of our medicine supply. Medicines that enter the United States through importation will not be subject to these same strong standards and, as a result, counterfeit, substandard or diverted, repackaged and adulterated drugs could be introduced into our secure drug supply chain."[163]

The FDA's position on importation is to a large extent a product of the lobbying power of the pharmaceutical industry.[164] [165] Drug industry groups' lobbying efforts influence Congress to create laws and regulations favorable to its business models and, in turn, ensure that the FDA enforces regulations that most protect it.[166] Thus, not only is the FDA a victim of "industry capture," but it bureaucratically perpetuates a self-regard as the "gold standard" in drug regulation and safety.[167] This dynamic is made possible by the unique regulatory arena of prescription drug manufacturing and marketing, where the regulator and regulated appear to have the same goal: the creation and distribution of as many safe and effective drugs to help as many people as possible.[168] Thus, even for those who insist that profit is the only goal of the pharmaceutical industry, the point here is not the sincerity of the industry but understanding the reputation it strives for and needs.[169] For this reputation, the industry looks to the FDA.

This bureaucratic paradigm, discussed in detail below, one created by the industry, is now endemic to the FDA's mission and helps maintain a high-priced captive market for prescription drugs. This framework of analysis was developed in "Reputation and Authority: The FDA and the Fight over U.S. Prescription Drug Importation" by Thomas J. Bollyky and Aaron S. Kesselheim.

FDA's public opposition to legislation and regulatory reforms on importation often relies on the argument that the agency does not have the resources to oversee the kinds of importation pathways that could lead to lower prices, while still protecting public health, and that the resources needed are too great.[170] Bollyky and Kesselheim explore how the FDA's position on importation is less about resources and public health and more about self-protective bureaucracy. They deconstruct what I believe are the bureaucratic consequences of the pharmaceutical industry's lobbying power in explaining the FDA's opposition to importation:

> "[...]FDA officials describe themselves as "the gold standard" for drug review — more thorough and rigorous about regulation than their counterparts — and, until recently, as able to fulfill their core institutional mandates without the cooperation of foreign counterparts."[171]

Thus, while the FDA has agreed to sign MOUs with many foreign drug regulators, accepting their inspections in lieu of its own, it will not accept the equivalence determinations of those same regulators because, according to Bollyky and Kesselheim, that would threaten the FDA's reputation and its funding. They state:

> "…[T]he FDA's limited use of equivalence determinations is unsurprising. In contrast to the European Commission ('EC'), where its Directorate-General for Industry and Enterprise is charged with coordinating regulatory protection and trade, the FDA has the consolidated statutory authority as the

> gatekeeper for ensuring the safety, quality, and efficacy of medicines. To sustain that authority and its funding, the FDA depends on its reputation for protecting consumers from unsafe drugs."
>
> "[...] FDA has resisted initiatives that might undermine that reputation and subordinate its gatekeeping mission to other policy objectives, such as lowering drug prices or facilitating *trade*."[172] Emphasis added.

Instead of "trade," the authors could have used the word "importation."

Unfortunately, Bollyky and Kesselheim accept the agency's position as a *fait accompli* and do not challenge its substantive flaws. They appear to recognize that the agency is not necessarily the Gold Standard anymore, but, because of its reputation and authority and, thus, its refusal to accept foreign drug approvals, they recommend a new permitted importation channel that they believe will not challenge the FDA:

> "[...]we suggest that a mechanism for U.S. prescription drug importation could be successfully used to reduce generic drug shortages and extreme price hikes among off-patent drugs that function like product shortages[...]"[173]

Their recommendation would allow imports of lower cost, foreign versions of FDA-approved drugs, mostly when a shortage exists in the U.S., but also in cases of when off-patent drugs are subject to severe price hikes. An example of such a drug is Gleostine, a brand name version of an FDA-approved drug called *lomustine*, an off-patent medication that treats cancer. These are drugs for which companies try to exploit marketing exclusivity rules to corner the market. In this case, a company called Next Source Biotechnology LLC secured these rights and launched Gleostine in 2016 with a price tag of about $750/pill. Before that launch, a Bristol Myers Squibb brand version called CeeNU was sold in the U.S. for about $50/pill, but it is no longer approved for marketing in the U.S. CeeNU, however, is approved for sale in Canada, costing about $25/pill.[174] Bollyky and Kesselheim believe these are the types of drugs we should import as a means to lower drug costs and that FDA might support this limited importation. Theirs is a commonsense and workable public policy to improve price competition for prescription drugs. However, it is unnecessarily limited to this subset of drugs and would leave much of the protectionism afforded drug manufacturers in place.

Bollyky and Kesselheim's approach does not address the main cost driver, which is patented drugs. Most expensive among those are biologics. According to a RAND Corporation analysis, prices for biologics in the U.S. are almost three times higher on average than in other OECD countries.[175] While that is lower than the overall price differentials estimated by RAND, with U.S. prices being 3.44 times higher, the impact on overall spending on biologics is greater.[176] Biologics usually cost between $10,000 - $30,000 and in some cases exceed $500,000 a year.[177] Almost all new patented cancer drugs are over $100,000.[178]

The FDA's leadership was famously cemented in the early 1960s when an FDA drug reviewer, Dr. Frances Kelsey, boldly prevented the approval of *thalidomide* in the U.S..[179] Thalidomide, used as a drug to treat morning sickness, was found to cause birth defects in babies born to women who had taken the drug while pregnant. It is estimated to have caused deformities in 10,000 babies worldwide.[180] Until recently, the mythologizing narrative held that only 17 babies in the U.S. were known to be affected.[181] Those cases were the result of the drug company distributing samples to doctors who gave them to their patients even though the drug was not approved.[182] An investigative article from 2020 by Katie Thomas at the New York Times indicates a much larger affected population.[183]

This history is often presented to showcase the superiority of U.S. drug regulators.[184] Dr. Kelsey's heroic efforts speak for themselves, but it was really subsequent lawmaking by Congress that forced the FDA to conduct much more stringent drug evaluations before approving new drugs for the market.

What is not often stated is that these same reforms to improve drug regulation happened in many other countries, too.[185] History also shows that U.S. drug companies lobbied to prevent these changes as well. An article published on the FDA's website about the agency's history clarifies this point:

> "As a result of the worldwide thalidomide disaster, countries around the world, including the United States, updated their drug regulatory systems and statutes. 'In next to no time,' recalled Frances Kelsey, 'the fighting over the new drug laws that had been going on for five or six years suddenly melted away, and the 1962 amendments were passed almost immediately and unanimously.'"[186]

We can recognize, simultaneously, the FDA's innovative success *and* the growth of foreign drug regulatory authorities. The latter now have comparable capacities for drug evaluation and may even be *better* at this point in regulation of the production of prescription drugs. In doing so, we can move beyond a protected marketplace where a mistaken presumption of FDA superiority helps keep drug prices high.

The global supply chains for brand name pharmaceuticals in other high-income countries allow for dynamic and safe parallel trade that would serve to substantially lower drug prices in the United States and equalize them across high income countries. The extent to which our drug supply relies on importation currently is enough to warrant serious reforms in the U.S.; that is to allow businesses, *other than drug manufacturers*, the ability to import drugs at lower prices from countries beyond Canada, most importantly from the European Union.

It is no longer defensible for the FDA to prevent this on the basis of drug safety.

4.5. Policy Recommendations for the Federal Government

This final section includes policy recommendations for the federal government given the findings in "Not Made in the USA."

- ❖ Require drug manufacturers to clearly identify the country where a drug's API and FDF originated.

Pharmaceuticals to make prescription drugs sold in the U.S. come from all over the world. This paper has shown that manufacturer labels already provide information making it possible to assess where drugs come from. However, it should be more straightforward for patients, providers, and policymakers to know from where the active pharmaceutical ingredients and finished formulations of prescription drugs purchased in U.S. pharmacies come. Also, the country in which a drug is merely *labeled* and *packaged*, if different from the place where the actual drug is *manufactured*, should not be identified as the place of manufacture, as is currently permissible under the Food, Drug, and Cosmetic Act.

To accomplish this, Congress should amend *Section 502 of the Food, Drug, and Cosmetic Act, 21 USC 352: Misbranded drugs and devices*. A drug label should make it clear to a patient where the drug's API and its finished formulation were manufactured.

Current law requires that a prescription drug label include the "name and place of business of the manufacturer, packer, or distributor…"

New legislation should require adding the following language: "and the countries of origin of the active pharmaceutical ingredients and the finished drug formulation and the country where the drug was labeled and packaged." Under these changes, the relevant Code of Federal Regulations (21CFR201) would state:

> "A drug or drug product (as defined in § 320.1 of this chapter) in finished package form is misbranded under section 502 (a) and (b)(1) of the act if its label does not bear conspicuously the name and place of business of the manufacturer or distributor; the countries of origin of the active pharmaceutical ingredients and the finished drug formulation; and the country where the drug was labeled and packaged."

- ❖ Mandate through legislation the publication of an annual FDA report showing clear and accurate data on where our drugs are made.

Congress should amend the FDCA to require an annual report from the FDA so that Americans know what percentage of FDA-approved drugs are not made domestically. This would not require the FDA to know the *volumes* of pharmaceutical imports. The report would simply list the name of every FDA-approved drug; its National Drug Code; the country its API or APIs are made in; the country of its final formulation; and the country where it is packaged for final dispensing.

- ❖ Through legislation, expressly allow importation of brand name drugs by companies, other than their manufacturers, from countries known to have similarly strong pharmaceutical regulations as the U.S., subject to rational regulatory safeguards.

Under current law, Section 804 of the FDCA, importation of commercial quantities of prescription drugs for re-sale without the authorization of the manufacturer is only permitted from Canada. Its relatively small size to the U.S., 38 million compared to 330 million, precludes long-term and meaningful parallel trade in pharmaceuticals with the United States. In contrast, the combined markets of Canada, Japan, the European Union, and the United Kingdom, have 667 million people — twice the U.S. population. If other high-income countries with strong pharmaceutical regulations are added, including Australia, Israel, New Zealand, Singapore, and Switzerland, the relevant market size is almost 700 million. Those regions and countries are also where most of our brand name drugs are manufactured. Section 804 must be amended to allow non-manufacturers importation from those countries, too.

The amendment to allow imports from this greater network of countries would be specific to brand name drugs manufactured in the listed countries.

Currently, Section 804 precludes the importation of biologics. The most expensive category of medical products on the market, biologics represent about 40% of all pharmaceutical expenditures,[187] but only about 2% of prescriptions written.[188] As previously mentioned, wholesale prices for biologics are on average almost three times higher in the U.S. than in the OECD.[189] Thus, Section 804 must be amended to permit the importation of biologics.

Ostensibly, the preclusion of biologics in Section 804 was due to the greater challenges in safe distribution of what are referred to as "large molecule" pharmaceuticals that are produced with living organisms and therefore require special technology to ship under temperature controls. Today, U.S. pharmacy benefit managers, such as Optum,[190] are already actively importing biologics, albeit under the authorization and with the cooperation of the manufacturers. A federal rule should require wholesale importers of biologic drugs to meet or exceed manufacturer specifications for safe, international shipping. Optum's marketing materials provide a roadmap to develop the standard).[191]

The current federal rule allowing wholesale importation under Section 804, requires that the U.S. importer only imports from a wholesaler that received the products for import directly from the manufacturer. This rule makes it easier for drug manufacturers to use inventory management to prevent unwanted distribution of their products from lower to high priced markets. The rule should be revised to allow the U.S. importer to import from a secondary wholesaler, as long as that wholesaler received the products from the wholesaler that first received the products from the manufacturer. This revision would maintain a closed distribution channel while allowing for the development of a competitive marketplace in pharmaceutical trade, similar to the European Union.

- ❖ Remove barriers and provide guidance to assist individual patients who seek to import brand name drugs pursuant to a valid prescription.

The Secretary of Health and Human Services is already seeking new ideas on expanding personal drug importation to help patients access lower drug prices internationally.[192]

The FDCA is very flexible to allow personal importation of lower-cost medicines. A few million Americans each year already import lower-cost medicine for personal use. While they are not charged or prosecuted for illegal imports, individuals purchase medicine, often over the Internet within a grey marketplace, receiving conflicting messages from regulators, industry-sponsored and non-profit organizations on what they should and shouldn't do.

Organizations like PharmacyChecker and the Canadian International Pharmacy Association provide guidance to patients and healthcare providers for those who choose to import medicine for personal use. Those private sector solutions are helpful, but a publicly or non-profit funded effort is needed to bring greater awareness and stakeholder acceptance of safe personal drug importation.

To maximize the utility of personal drug importation as a safe and accepted channel for drug affordability, the following is proposed:

1. Create an HHS task force with a diverse set of stakeholders to review best practices in safe personal drug importation and create FDA recommendations to the public. As part of its mandate, the task force would identify all current programs and channels of personal drug importation, assessing their strengths and weaknesses.

2. Revise the FDA's public communications to include useful recommendations for patients who choose to import a lower cost medicine for personal use and clarify that the agency will not

prevent the personal import of a brand name drug from licensed pharmacies in Australia, Canada, the European Union, Israel, Japan, New Zealand, Switzerland, Singapore, and the UK.

As a general model, the U.S. can look to Australia, in which personal importation is expressly legal and the government provides warnings and guidance.[193] As Australians do not face the same problems as Americans do with drug affordability, Australians' necessity for personal importation is not as widespread. Thus, the FDA would need to create more robust warnings and guidelines for patients in the United States.

- ❖ Instead of reactionary, mercantilist policies to bring drug manufacturing home, pursue greater global collaboration and coordination towards an international agreement to better regulate and ensure the safe manufacture and high quality of APIs.[194]

APIs are made all over the world and shipped globally to different drug companies for the manufacture of FDFs. This global competition has meant much lower cost generic drugs worldwide, including in the U.S. For reasons of national security, whether due to geopolitical tensions with China or reliance on foreign supplies during the pandemic, there is a new rallying cry for greater autarky with pharmaceuticals. A more longstanding, and less politically charged issue is that, for over 20 years, the FDA has been criticized for its inability to keep up with federal requirements on inspections and oversight of global API manufacturers.

In terms of national security, the U.S. should identify the greatest vulnerabilities and create practical contingency plans involving alternative suppliers or ramping up domestic production. The FDA has reported to Congress on the extent of our vulnerabilities, and they are not as great as the rhetoric on this issue. China accounts for 13% of all FDA registered API manufacturers, a significant but not overwhelming figure. As a matter of national defense policy, we need to identify alternative suppliers for those pharmaceutical ingredients and appropriate special funding and production plans to ramp up domestic manufacturing of the most critical pharmaceuticals.

Outside the above-mentioned national security issues, we must accept the reality of global pharmaceutical manufacturing. To maximize safety and minimize cost, the U.S. should set clear goals for international harmonization on API standards, cGMP, and distribution. The European Medicines Agency is already leading this effort, with the FDA as a participant.[195] FDA's MRAs with all EU countries on drug manufacturing, finalized in 2019, occurred because the FDA knows that the future lies in globally accepted standards and even shared regulatory authority.

Efforts to harmonize API quality standards have been ongoing for 20 years through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the Pharmaceutical Inspection Co-operation Scheme, and the World Health Organization. The FDA publishes a questions-and-answers document for the regulated industry called "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" that is the product of those efforts.[196]

The next step is for the FDA to prioritize working with those international forums and counterpart national drug regulators to create a global regulatory approval scheme for API manufacturers. The goal is for an API manufacturer, whether in Mumbai, Minneapolis, or Munich, to gain approval for international distribution based on one high standard. This will create efficiencies, improve safety, and reduce costs for American taxpayers.

APPENDIX A. INTERNATIONAL PRICE COMPARISONS 2018 MEDICARE PART D TOP SPEND DRUGS

INTERNATIONAL PRICE COMPARISONS 2018 MEDICARE PART D TOP SPEND DRUGS

Brand Name Drug	*Generic Name*	*Strength*	*Quantity*	*Average US Retail Price*	*Average International Online Pharmacy Price*	*Average Canadian Online Pharmacy Price*	*International Mail order Savings*	*Canadian Mail order Savings*
Eliquis	Apixaban	5mg	90 tablets	$853.20	$150.77	$203.62	82.33%	76.14%
Revlimid	Lenalidomide	10mg	90 tablets	$71,722.80				
Xarelto	Rivaroxaban	20mg	90 tablets	$1,648.80	$221.33	$326.10	86.58%	80.22%
Januvia	Sitagliptin Phosphate	100mg	90 tablets	$1,701.00	$161.16	$372.79	90.53%	78.08%
Lyrica	Pregabalin	75mg	90 tablets	$563.92				
Advair Diskus	Fluticasone Propion/Salmeterol	250mcg/50 mcg	180 doses	$1,187.64	$147.96	$358.99	87.54%	69.77%
Humira Pen	Adalimumab	40mg/0.4ml	3 cartons	$25,842.25				
Lantus Solostar	Insulin Glargine,Hum.Rec.Anlog	3ml	3 cartons	$1,479.18				
Imbruvica	Ibrutinib	140mg	90 tablets	$43,541.10	$9,967.14	$10,591.48	77.11%	75.67%
Symbicort	Budesonide/Formoterol Fumarate	160mcg/4.5mcg	3 inhalers	$1,322.16	$206.89	$325.98	84.35%	75.34%
Harvoni	Ledipasvir/Sofosbuvir	90mg/400 mg	84 tablets	$100,567.92	$70,513.83	$77,999.96	29.88%	22.44%
Novolog Flexpen	Insulin Aspart	100 units/mL	15 pens	$1,979.49				
Levemir Flextouch	Insulin detemir injection	100 units/mL	15 Pens	$1,672.00				
Ibrance	Palbociclib	125mg	63 capsules	$39,019.92	$19,947.98	$19,613.37	48.88%	49.73%
Zytiga	Abiraterone Acetate	500mg	180 tablets	$36,740.03	$12,329.64	$13,087.06	66.44%	64.38%

Spiriva	Tiotropium Bromide	18 mcg	90 capsules	$1,435.31	$137.93	$238.55	90.39%	83.38%
Trulicity	Dulaglutide	1.5mg/0.5 mL	3 cartons	$2,525.64				
Victoza 3-Pak	Liraglutide	18mg/3mL	3 cartons	$3,479.75				
Lantus	Insulin Glargine,Hum.Rec.Anlog	100 units/mL	3 cartons	$1,360.56				
Enbrel Sureclick	Etanercept	50mg/mL	3 cartons	$23,158.15				
Copaxone	Glatiramer Acetate	40mg/mL	3 cartons	$18,050.71	$4,894.68	$4,894.68	72.88%	72.88%
Humalog Kwikpen U-100	Insulin Lispro	100 units/mL	3 cartons	$1,627.23	$461.26	$461.26	71.65%	71.65%
Xtandi	Enzalutamide	40mg	360 capsules	$51,361.20	$12,991.57	$12,715.42	74.71%	75.24%
Latuda	Lurasidone HCl	40mg	90 tablets	$4,565.70	$433.33	$541.13	90.51%	88.15%
Breo Ellipta	fluticasone furoate and vilanterol	100/25mcg	3 inhalers	$465.06	$287.86	$348.98	38.10%	24.96%
Invega Sustenna	Paliperidone Palmitate	156mg	3 syringe	$6,760.78	$1,826.00	$2,221.39	72.99%	67.14%
Myrbetriq	Mirabegron	25mg	90 tablets	$1,493.10	$247.27	$249.98	83.44%	83.26%
Restasis	Cyclosporine	0.05%	180 vials	$2,083.74	$406.53	$801.43	80.49%	61.54%
Tradjenta	Linagliptin	5mg	90 tablets	$1,645.20	$192.41	$297.99	88.30%	81.89%
Tecfidera	Dimethyl Fumarate	240mg	168 capsules	$33,111.12	$6,070.34	$6,274.88	81.67%	81.05%
Jakafi	Ruxolitinib phosphate	5mg	168 tablets	$40,291.44	$8,678.48	$17,100.72	78.46%	57.56%
Pomalyst	Pomalidomide	4mg	63 capsules	$57,153.15				
Epclusa	Velpatasvir and sofosbuvir	400/100mg	84 tablets	$91,209.72	$57,102.66	$57,102.66	37.39%	37.39%

Lipitor	Atorvastatin Calcium	10mg	90 tablets	$1,167.30	$110.18	$225.26	90.56%	80.70%
Genvoya	elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide	150/150/200/10mg	90 tablets	$11,670.83	$4,517.62	$4,712.11	61.29%	59.62%
Synthroid	Levothyroxine Sodium	50mcg	90 tablets	$174.57	$31.05	$30.79	82.21%	
Triumeq	abacavir, dolutegravir, and lamivudine	600/50/300mg	90 tablets	$10,978.75	$4,096.19	$4,343.99	62.69%	60.43%
Linzess	linaclotide	290mcg	84 tablets	$1,567.80	$387.74	$513.32	75.27%	67.26%
H.P. Acthar	Corticotropin	80 units/mL	2 vials	$40,612.75				
Oxycontin	Oxycodone HCl	10mg	90 tablets	$485.51				
Lopressor	Metoprolol Succinate	50mg	90 tablets	$297.80	$49.92	$62.20	83.24%	
Novolog	Insulin Aspart	100 units/mL	3 vials	$934.77				
Janumet	Sitagliptin Phos/Metformin HCl	50/1000mg	90 tablets	$892.80	$118.51	$204.74	86.73%	77.07%
Vesicare	Solifenacin Succinate	5mg	90 tablets	$1,376.10	$138.72	$201.40	89.92%	85.36%
Invokana	Canagliflozin	100mg	90 tablets	$1,876.50	$294.61	$343.89	84.30%	81.67%
Creon	Pancrelipase	5000/25500/1600 units	300 tablets	$3,650.20				
Jardiance	empagliflozin	10mg	90 tablets	$1,845.00	$171.79	$307.35	90.69%	83.34%
Anoro Ellipta	umeclidinium and vilanterol inhalation powder	62.5/25mg	90 doses	$1,349.85	$275.43	$335.66	79.60%	75.13%
Ranexa	Ranolazine	500mg	180 tablets	$1,517.65	$416.34		72.57%	

Renvela	sevelamer carbonate	800mg	270 tablets	$2,027.70	$545.05	$496.64	73.12%	75.51%
Tivicay	dolutegravir sodium	50mg	90 tablets	$6,647.40	$2,044.14	$2,124.38	69.25%	68.04%
Pradaxa	Dabigatran Etexilate Mesylate	150mg	180 capsules	$1,663.20	$242.41	$394.97	85.43%	76.25%
Xifaxan	Rifaximin	550mg	56 tablets	$2,880.08	$745.88	$615.52	74.10%	78.63%
Tresiba Flextouch U-200	insulin degludec injection	100 units/mL	3 cartons	$1,820.34				
Aubagio	teriflunomide	14mg	84 tablets	$31,132.50	$6,939.16	$6,900.00	77.71%	77.84%
Ofev	nintedanib	150mg	180 tablets	$37,744.20	$7,327.48		80.59%	
Enbrel	Etanercept	50mg	3 cartons	$21,429.51	$5,990.77	$5,990.77	72.04%	72.04%
Letairis	Ambrisentan	5mg	90 tablets	$31,893.00				
Dexilant	Dexlansoprazole	60mg	90 tablets	$1,047.60	$270.17	$264.74	74.21%	74.73%
Forteo	Teriparatide	250mcg/mL	3 pens	$14,527.91				
Humira	Adalimumab	40mg/0.4mL	3 cartons	$25,842.25				
Toujeo Solostar	Insulin glargine	300 units/mL	3 cartons	$1,245.96				
Humalog	Insulin Lispro	100 units/mL	3 vials	$888.87				
Stelara	Ustekinumab	90mg/mL	3 syringes	$79,202.93				
Neurontin	Gabapentin	300mg	60 capsules	$506.25	$74.20	$83.99	85.34%	83.41%
Ventolin HFA	albuterol sulfate	90mcg	3 inhalers	$225.43	$58.20	$50.04	74.18%	77.80%
Esbriet	Pirfenidone	267mg	270 tablets	$10,600.97	$3,464.91	$4,524.93	67.32%	57.32%
Descovy	emtricitabine and tenofovir alafenamide	200mg/25mg	90 tablets	$6,510.63	$2,946.26	$3,029.36	54.75%	53.47%

Lumigan	Bimatoprost	0.01%	9mL	$757.30	$96.24	$170.99	87.29%	77.42%
Vimpat	Lacosamide	200mg	180 tablets	$3,467.79				
Gleevec	Imatinib Mesylate	400mg	30 tablets	$13,785.88	$2,204.38	$4,102.49	84.01%	70.24%
Levemir	Insulin Detemir	100 units/mL	3 vials	$1,152.35				
Spiriva Respimat	tiotropium bromide	2.5mcg	3 inhalers	$1,454.31	$269.37	$271.21	81.48%	81.35%
Norco	Hydrocodone/Acetaminophen	10mg/325 mg	120 tablets	$677.11				
Crestor	Rosuvastatin Calcium	10mg	84 tablets	$1,024.80	$82.51	$170.83	91.95%	83.33%
Incruse Ellipta	umeclidinium inhalation powder	62.5mg	3 inhalers	$1,255.41	$235.16	$230.59	81.27%	81.63%
Abilify	Aripiprazole	5mg	30 tablets	$1,076.38	$150.77	$155.49	85.99%	85.55%
Combivent Respimat	Ipratropium/Albuterol Sulfate	20/100mcg	3 inhalers	$1,364.13	$149.98	$149.98	89.01%	89.01%
Nexium	Esomeprazole Magnesium	40mg	90 capsules	$786.24	$140.30	$259.27	82.16%	67.02%
Klor-Con	Potassium Chloride	10meq	90 tablets	$54.50				
Entresto	Sacubitril and valsartan	24/26mg	84 tablets	$934.08	$340.95	$387.90	63.50%	58.47%
Cymbalta	Duloxetine HCl	60mg	30 capsules	$323.71	$64.89	$149.99	79.95%	53.67%
Shingrix	Zoster Vaccine Recombinant, Adjuvanted	0.5ml	1 vial	$195.60	$181.26	$181.26	7.33%	7.33%
Gilenya	Fingolimod HCl	0.5mg	84 tablets	$34,036.76	$8,837.81	$8,610.04	74.03%	74.70%
Opsumit	macitentan	10mg	90 tablets	$51,757.20	$9,768.99	$12,899.97	81.13%	75.08%
Novolog Mix 70-30 Flexpen	Insulin Aspart Prot/Insuln Asp	100 units/mL	3 cartons	$2,034.68				

Basaglar Kwikpen U-100	insulin glargine injection	100 units/mL	3 cartons	$1,050.66				
Mavyret	glecaprevir and pibrentasvir	100mg/40 mg	12 Packages	$44,776.50				
Brilinta	ticagrelor	90mg	168 tablets	$1,354.08	$359.08	$391.07	73.48%	71.12%
Bystolic	nebivolol hydrochloride	5mg	84 tablets	$540.96	$85.87	$162.59	84.13%	69.94%
Flovent HFA	fluticasone propionate inhalation aerosol	125mcg	3 inhalers	$836.91	$100.62	$186.48	87.98%	77.72%
Travatan Z	Travoprost	0.004(Percent%)	15mL	$1,408.98	$259.34	$241.75	81.59%	82.84%
Zetia	Ezetimibe	10mg	30 tablets	$427.91	$64.47	$81.49	84.93%	80.96%
Prilosec	Omeprazole	40mg	30 capsules	$350.00	$65.24		81.36%	
Tagrisso	osimertinib	80mg	90 tablets	$49,695.30	$31,561.97	$32,509.96	36.49%	34.58%
Afinitor	Everolimus	10mg	90 tablets	$86,864.40	$14,660.03	$22,616.75	83.12%	73.96%
Proair HFA	Albuterol Sulfate	100mcg	3 inhalers	$237.99	$105.69	$105.69	55.59%	55.59%
Renagel	Sevelamer Carbonate	800mg	90 tablets	$873.17	$193.24	$183.62	77.87%	78.97%
Sprycel	dasatinib	50mg	120 tablets	$41,528.89	$9,754.19	$10,823.50	76.51%	73.94%
Farxiga	dapagliflozin	5mg	84 tablets	$1,757.28	$193.16	$287.46	89.01%	83.64%
						AVERAGE	75.53%	70.18%

Sources: PharmacyChecker Research, 2021. Dataset chosen based on top Medicare spending in the year 2018. Prices collected in the year 2021. Average U.S. Retail price sourced from Goodrx.com, Drugs.com, and PharmacyChecker.com; Average International and Canadian pricing calculated based on those listed on PharmacyChecker.com. Canadian prices are those of drugs that are dispensed from pharmacies located in Canada only. As quantities may vary internationally,

International pharmacies in the PharmacyChecker Verification Program are not permitted to (and do not) ship refrigerated drug products to the U.S. Refrigerated product pricing is included, where applicable, to illustrate savings possible if and when refrigerated delivery is improved and meets the PharmacyChecker Verification Program standards.

APPENDIX B. COUNTRY OF ORIGIN ACCORDING TO THE CBP VS. FDA OF TOP MEDICARE PART D BRAND NAME DRUGS IN 2018

BRAND NAME	MEDICARE SPENDING 2018	FDA MADE IN	CBP MADE IN	MARKETING DRUG COMPANY
ELIQUIS	$4,992,184,164.40	USA	SWITZERLAND	Bristol-Myers Squibb & Pfizer
REVLIMID	$4,065,088,800.50	SWITZERLAND	SWITZERLAND	Celgene Corporation
XARELTO	$3,358,810,708.00	USA	GERMANY	Janssen Pharmaceuticals, Inc.
JANUVIA	$3,228,917,720.20	UK	ITALY	Merck Sharp & Dohme Corp.
LYRICA	$2,950,257,660.50	SINGAPORE	SINGAPORE	Pfizer
ADVAIR DISKUS	$2,394,014,929.40	UK	ENGLAND	GlaxoSmithKline LLC
HUMIRA PEN	$2,388,794,496.60	USA	USA	AbbVie Inc.
LANTUS SOLOSTAR	$2,370,490,821.50	GERMANY	GERMANY	sanofi-aventis U.S. LLC
IMBRUVICA	$1,867,207,012.50	USA	CHINA	Pharmacyclics LLC; Janssen Biotech, Inc.
SYMBICORT	$1,751,221,155.50	FRANCE	FRANCE	AstraZeneca
HARVONI	$1,726,263,039.20	IRELAND	IRELAND	Gilead
NOVOLOG FLEXPEN	$1,712,623,585.10	DENMARK	DENMARK	Novo Nordisk
LEVEMIR FLEXTOUCH	$1,584,105,949.80	DENMARK	DENMARK	Novo Nordisk
IBRANCE	$1,507,730,890.00	IRELAND	IRELAND	Pfizer Laboratories
ZYTIGA	$1,475,649,550.90	FRANCE	BELGIUM	Janssen
SPIRIVA	$1,425,533,898.50	GERMANY	GERMANY	Boehringer Ingelheim Pharmaceuticals, Inc.
TRULICITY	$1,360,642,452.00	IRELAND	IRELAND	Eli Lilly and Company
VICTOZA 3-PAK	$1,341,681,067.80	DENMARK	DENMARK	Novo Nordisk

LANTUS	$1,253,375,347.20	GERMANY	GERMANY	sanofi-aventis U.S. LLC
ENBREL SURECLICK	$1,247,769,463.30	USA	USA	Amgen
COPAXONE	$1,208,097,769.30	USA	ISRAEL	Teva Neuroscience, Inc.
HUMALOG KWIKPEN U-100	$1,199,656,303.70	USA	USA	Lilly
XTANDI	$1,182,615,333.30	USA	USA	Astellas Pharma US
LATUDA	$1,172,672,481.00	JAPAN	JAPAN	Sunovion
BREO ELLIPTA	$1,159,269,757.70	USA	USA	GlaxoSmithKline LLC
INVEGA SUSTENNA	$1,066,610,505.70	BELGIUM	IRELAND	Janssen
MYRBETRIQ	$1,063,585,890.00	JAPAN; IRELAND	JAPAN; IRELAND	Astellas Pharma US, Inc.
RESTASIS	$1,058,506,137.70	USA	USA	Allergan
TRADJENTA	$1,043,195,403.10	GERMANY	GERMANY	Boehringer Ingelheim Pharmaceuticals, Inc.
TECFIDERA	$1,019,481,294.40	USA	SWITZERLAND	Biogen
JAKAFI	$925,013,339.45	USA	USA	Incyte Corporation
POMALYST	$911,338,941.04	SWITZERLAND	SWITZERLAND	Celgene Corporation
EPCLUSA	$896,454,302.85	IRELAND	IRELAND	Gilead Sciences, Inc.
LIPITOR	$881,065,067.26	Multiple Countries	IRELAND	IRELAND
GENVOYA	$871,858,538.09	CANADA	CANADA	Gilead Sciences, Inc.
SYNTHROID	$828,162,512.18	USA, IRELAND	USA, FRANCE, ITALY, JAPAN, MEXICO, GERMANY	Abbot Laboratories
TRIUMEQ	$764,629,132.10	USA	USA	ViiV Healthcare Company
LINZESS	$761,658,895.28	IRELAND; UK	IRELAND; UK	AbbVie and Ironwood Pharmaceuticals, Inc.

H.P. ACTHAR	$724,638,118.93	USA	USA	Questcor Pharmaceuticals
OXYCONTIN	$711,006,196.30	USA	USA	Purdue Pharma LP
LOPRESSOR	$705,396,295.30	USA	SPAIN	Validus Pharmaceuticals
NOVOLOG	$694,913,262.07	DENMARK	DENMARK	Novo Nordisk
JANUMET	$692,159,591.60	UK	UK	Merck Sharp & Dohme Corp.
VESICARE	$691,720,521.79	USA	IRELAND	Astellas Pharma US
INVOKANA	$671,727,313.53	ITALY; PUERTO RICO	BELGIUM	Janssen Pharmaceuticals, Inc.
CREON	$668,508,828.37	GERMANY	GERMANY	AbbVie Inc.
JARDIANCE	$668,459,355.87	ITALY	ITALY	Boehringer Ingelheim Pharmaceuticals, Inc.
ANORO ELLIPTA	$666,541,776.00	USA	USA	GlaxoSmithKline LLC
RANEXA	$658,259,298.44	GLOBALLY	GLOBALLY	Gilead
RENVELA	$654,147,390.98	UK	UK	SANOFI Genzyme Corporation
TIVICAY	$642,056,270.21	JAPAN	JAPAN	ViiV Healthcare Company
PRADAXA	$637,564,815.62	GERMANY	GERMANY	Boehringer Ingelheim
XIFAXAN	$633,453,580.70	CANADA	CANADA	Salix Pharmaceuticals, Inc.
TRESIBA FLEXTOUCH U-200	$627,964,946.53	DENMARK	DENMARK	Novo Nordisk
AUBAGIO	$627,062,230.08	GERMANY	GERMANY	SANOFI Genzyme Corporation
OFEV	$618,635,441.84	GERMANY	GERMANY	Boehringer Ingelheim Pharmaceuticals, Inc.
ENBREL	$611,605,535.46	USA	USA	Amgen
LETAIRIS	$608,195,650.13	CANADA	CANADA	Gilead
DEXILANT	$601,789,192.16	JAPAN/GERMANY	JAPAN/GERMANY	Takeda

FORTEO	$599,576,421.55	FRANCE	AUSTRIA	Lilly USA, LLC
HUMIRA	$596,366,042.85	USA; ITALY	USA (PUERTO RICO); SINGAPORE; GERMANY	AbbVie Inc.
TOUJEO SOLOSTAR	$596,026,240.76	GERMANY	GERMANY	Sanofi-Aventis U.S. LLC
HUMALOG	$589,288,819.45	USA	USA	Lilly
STELARA*	$582,683,696.71	USA; SWITZERLAND	USA; SWITZERLAND	Janssen Biotech, Inc.
NEURONTIN	$579,940,201.97	INDIA	INDIA	Pfizer
VENTOLIN HFA	$574,608,767.94	UK	UK	GlaxoSmithKline LLC
ESBRIET	$571,407,727.59	USA	USA	Genentech, Inc.
DESCOVY	$568,751,710.66	CANADA	CANADA	Gilead Sciences, Inc.
LUMIGAN	$548,708,659.54	USA	USA	Allergan
VIMPAT	$545,362,956.28	USA	USA	UCB, Inc.
GLEEVEC	$539,684,275.87	GERMANY	IRELAND	Novartis
LEVEMIR	$538,215,607.69	DENMARK	DENMARK	Novo Nordisk
SPIRIVA RESPIMAT	$529,512,525.92	GERMANY	GERMANY	Boehringer Ingelheim Pharmaceuticals, Inc.
LORCET	$529,426,439.49	USA	USA	Mayne Pharma
CRESTOR	$527,275,103.59	USA	UK	AstraZeneca
INCRUSE ELLIPTA	$517,467,101.90	USA	USA	GlaxoSmithKline LLC
ABILIFY	$507,896,142.19	JAPAN	JAPAN	Otsuka America Pharmaceutical, Inc.
COMBIVENT RESPIMAT	$507,498,092.26	GERMANY	GERMANY	Boehringer Ingelheim
NEXIUM	$506,138,795.93	SWEDEN	FRANCE	AstraZeneca
KLOR-CON	$500,342,391.44	USA	USA	Upsher Smith

ENTRESTO	$476,575,743.08	SINGAPORE	SINGAPORE	Novartis Pharmaceuticals Corporation
CYMBALTA	$471,161,117.21	USA	USA	Eli Lilly
SHINGRIX	$470,758,395.75	BELGIUM	BELGIUM	GlaxoSmithKline
GILENYA	$470,215,655.42	SWITZERLAND	SWITZERLAND	Novartis Pharmaceuticals Corporation
OPSUMIT	$468,822,598.28	SWITZERLAND	SWITZERLAND	Actelion Pharmaceuticals US, Inc.
NOVOLOG MIX 70-30 FLEXPEN	$465,998,078.48	DENMARK	DENMARK	Novo Nordisk
BASAGLAR KWIKPEN U-100	$465,157,479.09	USA	USA	Eli Lilly and Company
	$461,337,390.85	IRELAND	IRELAND	AbbVie Inc.
BRILINTA	$424,147,174.95	SWEDEN	BELGIUM	AstraZeneca Pharmaceutical
BYSTOLIC	$406,228,393.84	IRELAND	IRELAND	Allergan
FLOVENT HFA	$400,675,877.63	FRANCE	FRANCE	GlaxoSmithKline LLC
TRAVATAN Z	$393,794,154.41	USA	USA	Alcon Laboratories Inc
ZETIA	$392,719,405.97	USA	SINGAPORE	Merck Sharp & Dohme Corp.
PRILOSEC	$389,696,704.42	USA	IRELAND	AstraZeneca
TAGRISSO	$387,940,689.67	SWEDEN	SWITZERLAND	AstraZeneca
AFINITOR	$386,491,662.51	SWITZERLAND	SWITZERLAND	Novartis Pharmaceuticals Corporation
PROAIR HFA	$377,179,823.13	IRELAND	IRELAND	Teva Respiratory
SEVELAMER CARBONATE	$374,445,195.52	UK	UK	Genzyme Corporation
SPRYCEL	$372,249,027.07	SWITZERLAND	SWITZERLAND	Bristol-Myers Squibb
FARXIGA	$356,573,700.23	IRELAND	IRELAND	AstraZeneca Pharmaceuticals LP

APPENDIX C. UNDERSTANDING DRUG LABEL LANGUAGE

As explained in Section 2.2., the FDA considers the location of a drug's final formulation (FDF) and/or packaging as its origin. Whereas the CBP designates a drug's country of origin as that where the API was manufactured.

Some prescription labels are very clear about countries of manufacture. As shown on a U.S. label of the drug Januvia

SOURCE: U.S. NATIONAL LIBRARY OF MEDICINE, 2021

(sitagliptin), marketed by Merck & Co. Inc., there are three statements about manufacturing location:

1. Manuf. by: Merck Sharp & Dohme LTD, Cramlington, Northumberland, UK NE23 3JU.
2. Sitagliptin (active ingred.) Made in Italy.
3. Formulated in UK.

The API, *sitagliptin*, was made in Italy and the FDF was made in the UK.

- ❖ What can we conclude based on our knowledge of the FDA and CBP's differing definitions of country of origin?
  - ➢ The FDA views Januvia as imported from the UK.
  - ➢ The CBP views Januvia as imported from Italy.

To meet FDA labeling requirements, only the first line was necessary: "Manufactured by: Merck Sharp & Dohme LTD, Cramlington, Northumberland, UK NE 23 3JU." In this case, although not required by the FDA, MSD provides the location of the manufacturing plant. They could have chosen to list only the corporate office address.

Under the Tariff Act, the Januvia label must include "Made in Italy" because Italy is where the API is made. If Merck had not published "Made in Italy," it would have violated the Tariff Act. Although not as clear cut, failing to include "Made in Italy" would also be deemed a violation of the FDCA misbranding provisions, which require truthfulness and compliance with labeling laws.

The use of the phrase “Manuf. by” is short for “manufactured by.” Its use is surprising. Recall that the CBP views “Manufactured by” as interchangeable with “Made in” or “Product of.” That is where the API was made, according to CBP. Yet the API of this drug was made in Italy. In this case, it is likely acceptable to CBP because of the specificity of all manufacturing locations: “Formulated in UK” and “Sitagliptin (active ingred.) Made in Italy.”

SOURCE: U.S. NATIONAL LIBRARY OF MEDICINE, 2021

Bladder relaxant drug Vesicare provides a good example of how previous PharmacyChecker research (mentioned in the Preface) had not fully considered FDA and CBP rules. In that initial research, conducted in 2017, the goal was simply to determine the FDF’s country of manufacture — not its API. The Vesicare label reads “Product of Ireland,” and thus was categorized as an imported drug in the earlier research. “Not Made in the USA” considers the language “Product of Ireland” a requirement of the CBP because its API was made in Ireland. In contrast, the FDA views this drug as manufactured domestically. The label alone was not sufficient to determine that. Other details about its manufacturing were found in the FDA’s Labeling Package Insert for Vesicare:

> “Manufactured by:
>
> Astellas Pharma Technologies, Inc.
>
> Norman, Oklahoma 73072
>
> Marketed by:
>
> Astellas Pharma US, Inc.
>
> Deerfield, Illinois 60015-2548

Marketed and Distributed by:

GlaxoSmithKline

Research Triangle Park

North Carolina 27709

© 2005 Astellas Pharma US, Inc.

& GlaxoSmithKline"[197]

Indicative of the global nature of pharmaceutical companies is the fact that Astellas Pharma is based in Tokyo, Japan and GlaxoSmithKline is based in London, UK.

The language above distinguishes between manufacturing, marketing, and distribution. Astellas Pharma Technologies, Inc. is a manufacturing establishment, located in Oklahoma, and, by the FDA definition, it is where the FDF of Vesicare was "made" (finished or packaged). Why is there no statement reading "Product of Ireland" or Ireland at all on FDA's label information? The FDA's information is not the *manufacturer's* label on an imported product, and it is therefore not required.

The label of the insulin drug Humalog (*insulin lispro injection*), marketed by Lilly USA, only references the United States. Specifically, it identifies the name of the company marketing the product and its address:

SOURCE: U.S. NATIONAL LIBRARY OF MEDICINE, 2021

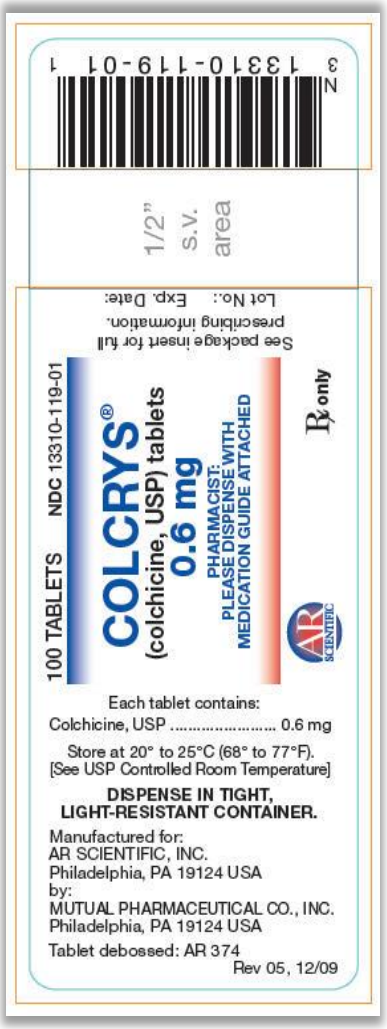
"Marketed by: Lilly USA, LLC Indianapolis, IN 42685"

In doing so, Eli Lilly meets the requirements of the FDA. Its label does not read "manufactured by," "product of," "Made in,'' or any other claim to identify the manufacturing source. Nonetheless, Humalog must be manufactured domestically. If it is not, this labeling would place Lilly in violation of the Tariff Act and the drug would be misbranded due to false and misleading labeling.

Why did Eli Lilly not use the claim “Made in the U.S.A.'' or even “manufactured by” and then give the U.S. address where the drug was finished? One reason could be that Humalog contains enough foreign components, which would pose an obstacle to the FTC Act standard of “all or virtually all” of the contents being domestically sourced, making a “Made in the U.S.A.” claim untenable. Humalog contains a patented delivery system for its active ingredient, *insulin lispro*. If the insulin was produced domestically but the delivery system -- or most of its components -- were made outside the U.S., then this, too, could risk violation of the Tariff Act.

Most drugs that both the FDA and CBP consider domestically manufactured are labeled using the words “Manufactured by:” followed by a U.S. address. If a drug’s API was made outside the U.S., unless it was “substantially transformed” during a domestic manufacturing process, then a drug manufacturer could not make the claim “manufactured by: [U.S. location]” without mentioning the other relevant country.

In some cases, when the product is “manufactured <u>for</u>” a marketing drug company “by” another manufacturing drug company, domestically, the labels may make such a distinction. See Colcrys (*colchicine*).



SOURCE: U.S. NATIONAL LIBRARY OF MEDICINE, 2021

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