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the  
**PRUDENT**  
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## How Safe ARE Drugs Made Outside the USA?

### The Problems:

1. Millions of Americans go without filling a prescription because they cannot afford it.
2. Many drugs sold in the United States can be obtained more cheaply in other countries.
3. Importing medication for personal use has been a staple of prescription drug savings for decades.
4. It's nearly impossible to sort out the origin of prescriptions (active ingredient(s) and final product).

Over the last thirty years, the pharmaceutical industry has created a false narrative that imported drugs are inherently NOT SAFE or COUNTERFEIT. Utilizing scare techniques, the lobbying group Pharmaceutical Researchers and Manufacturers of America (PhRMA) created companies with appealing names like Partnership for Safe Medicines, Alliance for Safe Online Pharmacies, and programs for the National Association of Boards of Pharmacies. PhRMA has spent millions of dollars shaping the views of Americans with misinformation. And then, and you have heard this before in this publication, the FDA seems to be in bed with Pharma on the issue of drug importation. The FDA's basic communication is that personal importation of drugs from pharmacies located in Canada and other countries is unsafe and technically illegal.

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.

- Stephen Salant, Professor Emeritus of Economics, University of Michigan

# PharmacyChecker

In 2002, Tod Cooperman, MD (also creator of ConsumersLab) founded PharmacyChecker. This interactive website directs patients to the lowest prices on prescription medication among licensed USA and international pharmacies. They are the only independent company monitoring and verifying the credentials of international online pharmacies and comparing prices of the prescription drugs available from these licensed pharmacies.



## The Study

Over the last two years, PharmacyChecker set out on an ambitious project to research the manufacturing locations of branded prescription drugs sold in the USA, their safety, and prices. On January 5, 2022, PharmacyChecker published “Not Made in the USA.” Gabriel Levitt, president of PharmacyChecker and Lucia Mueller, vice president of operations and communications are the co-authors of this 67-page study with 71 references. The report verifies “countries of manufacture” for the top 100 drugs by total expenditures for Medicare part D in 2018. Where there were generic drugs listed, they looked at the brand name product to assess the manufacturing origin of that drug. Eighty-five of the 100 drugs 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 USA National Library of Medicine. Where those labels were ambiguous, researchers looked to the FDA Labeling Package Insert drug information. 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 Final Drug Formulation (FDF) and the Active Pharmaceutical Ingredients (API). For example, in the case of the drug Januvia (sitagliptin), the API is made in Italy and the FDF in the UK.

## What they found

- A large majority of the top 100 drugs in Medicare Part D are branded products produced outside the USA:
  - 68% of finished drug formulations (FDFs = the final drug product prescribed to a patient by a medical professional) are produced outside the USA.
  - 78% of active pharmaceutical ingredients (API= the key components of a medicine that produce the intended effects in the body) are produced outside the USA.
- Since a large majority of prescription drugs sold in the USA are made with foreign APIs, tracking where they originate and the quality in those facilities is an important public health issue.
- Almost all imported brand name drugs are made in high-income countries with manufacturing safety practices equal or superior to those in the United States. Included are the European Union, Canada, Japan, Singapore, Switzerland, the United Kingdom, and India. 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 USA. With one exception in the 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.

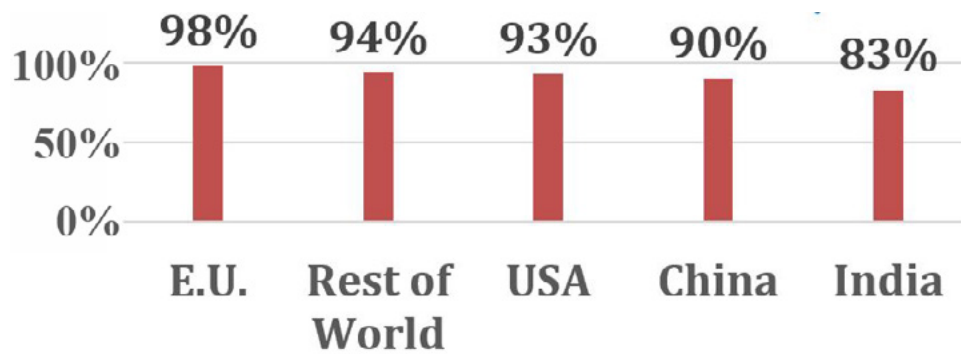
- In contrast, many generic drugs are comprised of ingredients from China and India, indicating that national security vulnerabilities are fewer for branded than generic drugs.
- **Of those drugs from the dataset that are accessible online, average international mail order prices were 75.53% lower than average USA pharmacy prices. Average prices of drugs only shipped from Canadian online dispensing pharmacies were 70.18% lower than average USA pharmacy retail prices.**
- The FDA and Customs and Border Protection (CBP)—the two agencies tasked with USA drug importation— have markedly different definitions for assigning country of origin of drugs. To CBP, the country in which the API is made is the country of origin. To the FDA, the country where the final formulation of a drug occurs is the drug’s country of origin.

### Price Comparisons 2018 Medicare Part D Top Spend Drugs

Brand Name	Generic Name	FDA Made In (Final Drug Product)	Customs Border Protection Made In (Active Pharmaceutical Ingredients)	Strength	Quantity	Average US Price	Average Canadian Online Price	% Savings by Utilizing Canadian mail order vs USA
Eliquis	apixaban	USA	Switzerland	5 mg	90 tablets	\$853.20	\$203.62	76%
Xarelto	rivaroxaban	USA	Germany	20 mg	90 tablets	\$1648.80	\$326.10	80%
Januvia	sitagliptin phosphate	UK	Italy	100 mg	90 tablets	\$1701.00	\$372.79	78%
Advair Diskus	fluticasone propionate/ salmeterol	UK	England	250mg/ 50 mg	180 doses	\$1187.64	\$358.99	70%
Symbicort	budesonide/ formoterol fumarate	France	France	160mcg/ 4.5mcg	3 inhalers	\$1322.16	\$325.98	75%
Zytiga	Abiraterone acetate	France	Belgium	500mg	180 tablets	\$36,740.03	\$13,087.06	64%
Myrbetriq	mirabegron	Japan Ireland	Japan Ireland	25mg	90 tablets	\$1493.10	\$249.98	83%

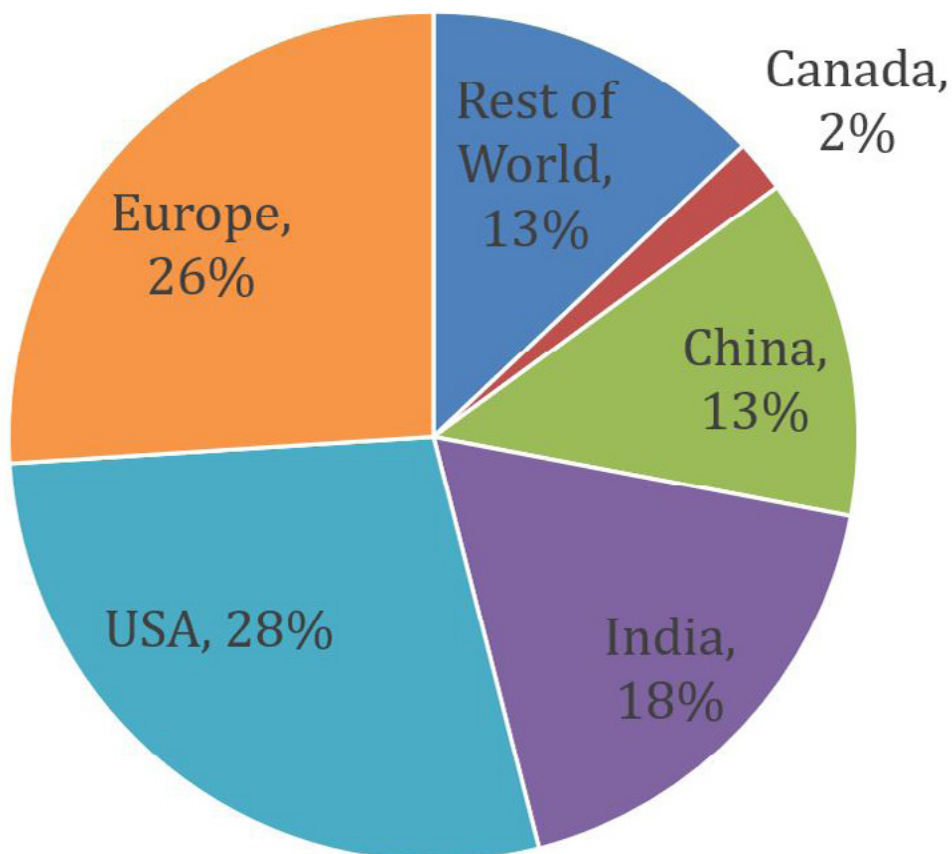
Adapted from Not Made in the USA, Appendices A and B

### Percentage of Drug Manufacturing Facilities with Acceptable Final Outcomes



Adapted from "Not Made in the USA" Fisher, A. C., Viehmann, A., Ashtiani, M., Friedman, R. L., Buhse, L., Kopcha, M., & Woodcock, J. (2020). Quality testing of difficult-to-make prescription pharmaceutical products marketed in the US. JAMA Network Open, 3(8), e2013920. <https://doi.org/10.1001/jamanetworkopen.2020.13920>

### Manufacturing Sites of APIs for US Market by Country or Region



Safeguarding pharmaceutical supply chains in a global economy. (2019, October 29). USA Food and Drug Administration.

## PharmacyChecker's 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 USA, 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.



### MY TAKE

- In this era of Big Pharma and FDA obfuscation, “Not Made in the USA” sheds light onto the origins, safety, and pricing of branded drugs consumed in the USA.
- Most of the commonly prescribed, expensive branded drugs in the USA are manufactured in high-income countries with manufacturing safety practices equal or superior to those in the United States. In terms of supply chain availability (yes, I am still hoarding Charmin), almost all of these foreign countries are considered friendly democracies.
- The European Union’s FDA equivalent, the European Medicines Agency (EMA) has led global regulatory cooperation on pharmaceutical manufacturing. The EMA, in addition to providing non-binding advice to its 27 member states has agreements to share drug evaluations with Australia, Canada, Israel, Japan, New Zealand, and Switzerland.
- For generic drugs (90% of our prescriptions), this report is sobering. Brand name drugs are likely to be of higher quality than generics. That is because branded finished products and their active pharmaceutical ingredients are mostly made in countries with the strongest regulations for pharmaceutical manufacturing while a significant percentage of the APIs of generics are manufactured in India and China.
- For those skeptical of prescribing from online pharmacies, this study may offer evidence for changing prescribing behaviors.
- My experiences with utilizing PharmacyChecker.com for my own family’s use and for my patients has meant big money saving and positive encounters.

# Antibody Testing for Covid-19 Immunity

## Oh, That It Were So Simple!

Initially in the pandemic, there was a sense that measuring antibody levels would predict who was protected from repeat infection. As Covid-19 vaccines came into play, patients wanted answers about the effectiveness of their jab. What is the role of antibody testing in the general population? Here's what we know:

- In May of 2021, the FDA reminded the public and health care providers that results from currently authorized SARS-CoV-2 antibody tests should not be used to evaluate a person's level of immunity or protection from Covid-19 at any time. They reiterated that stance in September.
- In spite of these warnings, some clinicians are routinely testing their patients for Covid-19 antibodies. Epitome Risk Solutions markets a \$170 at-home neutralizing antibody assay that consumers can order online. Their website proclaims, "The test will tell you if your immune system is still effective in fighting Covid-19 after a vaccination or previous infection."
- The fundamental concern with Epitome's test and that of all Covid-19 serology assays is the concept of "*correlates of protection*." Which antibodies guard against Covid-19? How high do the levels need to be? How long will these antibodies provide protection? In December of 2021, we simply do NOT have practical answers to these questions.
- Dr. Doria Rose (NIH) in an email to JAMA on October 21, 2021 noted that "antibodies that bind to the Covid-19 spike protein do correlate with protection. But it's not a simple relationship—there is no clear titer at which you can say whether a particular patient is protected."
- The other argument against antibody testing for immunity is that circulating antibodies do not give a complete picture of Covid-19 immunity. Memory B and T cells are the immunological components that are associated with protection against severe disease.
- Dr. Paul Offit, Children's Hospital of Philadelphia, who served on the FDA Vaccine Advisory Committee, has commented that reinfection with the Covid-19 virus activates memory B cells to differentiate into antibody-secreting cells. "Because the process can take 3-5 days, it does not stop Covid-19 infection from occurring, but it does tamp down severe disease. And that is a success story."
- We do know that vaccine immunity wanes with time and it wanes more quickly in older individuals than in younger populations.
- The Israeli experience of a significant number of breakthrough infections among fully vaccinated seniors six months and beyond after immunization refutes some of the B and T cell support for the "beyond the antibody immunity" argument.



## MY TAKE

Ordering antibody testing on most patients is fraught with potential disaster: false reassurance on one end and unnecessary angst on the other. The omicron surge further muddies the antibody testing waters. Unless there is a clear reason – like someone is immunosuppressed – don't do it!

### *Prudent Prescriber*

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