Statement on

A Resilient U.S. Drug Supply: Current & Emerging Vulnerabilities

at the House Hearing on

Chronic Drug Shortages in the United States

Statement before the

Committee on Ways & Means
United States House
Congress of the United States
Tuesday, February 6, 2024, at 10:00 a.m.
1100 Longworth House Office Building.

Statement of

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Thank you Chairman Smith, Ranking Member Neal, and other members of the House Committee on Ways & Means for this opportunity to address "A Resilient U.S. Drug Supply: Current & Emerging Risks."

I am Stephen W. Schondelmeyer, a Professor of Pharmaceutical Management & Economics at the University of Minnesota where I serve as Co-Principal Investigator for the Resilient Drug Supply Project (RDSP). In addition, I am Director of the *PRIME* Institute which focuses on research and policy issues related to the pharmaceutical market and its impact on society. These remarks are my own views based upon my research and experience in studying the pharmaceutical marketplace for the past fifty years. During my career, I have had the opportunity to interact with many federal entities that shape and influence our nation's healthcare system including the Department of Health and Human Services (DHHS), many of its divisions such as FDA, CMS, ASPE, ASPR, BARDA, as well as other federal agencies such as the FTC, DOJ, GAO, and OMB.

This hearing on chronic drug shortages in the United States will explore reasons for the long-term presence of drug shortages and the impact they have had on patients and the U.S. healthcare system. My remarks will address those issues as well as emerging vulnerabilities in the market infrastructure that are challenging the resilience of the U.S. drug supply.

First, let me point out that the relatively recent COVID-19 pandemic is not responsible for the chronic presence of drug shortages in the U.S., although COVID-19 has exposed and highlighted several new and emerging vulnerabilities including geopolitical risk, quality of production issues, and potential trade barriers.

The Nature of Chronic Drug Shortages and Why They Matter?

A reliable U.S. drug supply is an issue of public health, national security, and economic importance. Americans depend on a safe, accessible, and affordable drug supply for both personal and public health. When needed drugs are inaccessible for any reason, Americans suffer consequences such as lost days of work, disease progression and complications, increased emergency room visits, hospitalizations, and even premature death. *A robust drug supply chain is critical infrastructure for the health and well-being of the entire country, as well as the world.*

Life-threatening, critical drug shortages can, and do, occur in the U.S. market. For decades, the U.S. market has experienced substantial shortages of critical pharmaceuticals that can mean life or death for patients. Market forces alone have proven insufficient to resolve these challenges and have failed to provide a consistent drug supply chain. The COVID-19 pandemic did make issues in our upstream drug supply chain more visible. During the pandemic, there has been an increase in demand for many pharmaceuticals paired with numerous disruptions in supply chains. This has

further exposed systemic vulnerabilities in the pharmaceutical supply chain in the United States and around the globe. Even as we begin to emerge from the COVID-19 pandemic, the number of drug shortages has not abated. In fact, a recent Senate hearing (March 2023) reported that "Drug shortages are increasing, lasting longer, and impacting patient care."[1] Between 2021 and 2022, new drug shortages increased by nearly 30 percent. By the fourth quarter of 2023 the ASHP reports a total of 301 current drug shortages, near an all-time high for active drug shortages in the U.S.[2]

In the United States we have tracked drug shortages for nearly three decades and the literature has reported on specific drug shortages well before our tracking systems were initiated.[3] Over the past decade, there have been 170 to more than 300 national active drug shortages at any point in time. In the fourth quarter of 2023, the American Society of Health-System Pharmacists (ASHP) reported 301 active drug shortages.[4] This level of drug shortages and consequences for Americans is clearly not acceptable.

When a patient does not get a critical acute drug in a timely manner (i.e., minutes to hours to days) the consequence can be serious leading to emergency room visits, hospitalization, or even premature death. In addition to the clinical impact on patients, there are economic costs for patients, providers, health systems, distributors, and other stakeholders. Health systems have been estimated to incur extra costs due to shortages for purchasing alternate products, adding staff, and notification and training of healthcare personnel.[5] These added costs may be as high as $230 million[6] to $359 million per year or more.[7]

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[1] Chairman Gary Peters, United States Senate Committee on Homeland Security & Governmental Affairs, HSGAC Majority Staff Report, Short Supply, The Health and National Security Risks of Drug Shortages, March 2023, p. 5.
[2] Fox, E, National Drug Shortages, Active Shortages by Quarter – 10 Year Trend, University of Utah Drug Information Service, American Society of Health-System Pharmacists, found on February 3, 2024 at: https://www.ashp.org/drug-shortages/shortage-resources/drug-shortages-statistics.
[3] Fox, E, Tyler L, Managing drug shortages: Seven years' experience at on health system, Am J Health-Syst Pharm, Vol. 60, Feb. 1, 2003, pp. 245-253.
[4] Fox, E, National Drug Shortages, Active Shortages by Quarter – 10 Year Trend, University of Utah Drug Information Service, American Society of Health-System Pharmacists, found on February 3, 2024 at: https://www.ashp.org/drug-shortages/shortage-resources/drug-shortages-statistics; see, also: Fox, E, National Drug Shortages, New Shortages by Year, January 2001 to December 2023, % Injectable, University of Utah Drug Information Service, American Society of Health-System Pharmacists, found on February 3, 2024 at: https://www.ashp.org/drug-shortages/shortage-resources/drug-shortages-statistics.
[5] Shukar S, Zahoor F, Hayat K, Saeed A, et al., Drug Shortage: Causes, Impact, and Mitigation Strategies, Frontiers in Pharmacology, Vol. 12, July 2021, found at: https://www.frontiersin.org/articles/10.3389/fphar.2021.693426/full.
[6] Rapaport L, Drug shortages may add $230 million to annual U.S. drug costs, Reuters Health, Sept. 10, 2018, found at: https://www.reuters.com/article/us-health-drug-shortages-pricing/drug-shortages-may-add-230-million-to-annual-u-s-drug-costs-idUSKCN1M12LC/.
[7] Gu A, Wertheimer AI, Brown B, Shaya FT. Drug Shortages in the US–Causes, Impact, and Strategies. (2011). Inov Pharm. Vol 2, p. 6.

Virtually everyone in America has used, or needed, prescription drugs at some point in their lifetime. In 2021, Americans took about 189 billion daily doses of prescription drugs and 90.7% of those doses were generic products vulnerable to drug shortages.[8] Most, but not all, drug shortages involve generic drug products which account for only 19% of invoice-level spending on prescription drugs while branded drug products account for 81% of invoice-level spending on prescription drugs, but only 9.3% of prescriptions by volume.[9] For this reason, assessments of the impact of drug shortages should be based on the volume of daily doses affected and the number of Americans impacted. Additionally, drug shortages tend to be found most often in drug products that are generics (84%), injectables (67%), and highly-concentrated markets with few suppliers.[10]

Chronic drug shortages continued even during the COVID-19 pandemic, and several emerging changes in the structure of the pharmaceutical market were exposed and highlighted new vulnerabilities in the upstream U.S. drug supply chain. I will briefly describe each of these vulnerabilities including geopolitical risk, quality of production issues, and potential trade barriers.

Geopolitical Risk & Drug Supply Resilience

Geopolitical risk is a term that encompasses vulnerabilities in the upstream drug supply chain due to geographic location, political orientation, or both for the country where key stages of pharmaceutical production are performed. Among these key stages are production of key starting materials, manufacture of active pharmaceutical ingredients (API), and manufacture of finished dosage forms (FDF).

A stable drug supply relies on complex interdependencies in international relations, both commercially and politically. The United States is heavily dependent on foreign manufacturers for its active pharmaceutical ingredients and finished products, particularly China and India. About 45% of finished dose form units and about 60% the active pharmaceutical ingredients (API) in drug products consumed in the U.S. market come from India and/or China. This level of concentration of drug production in specific geographic areas poses significant problems in the face of natural disasters or pandemics, accidental or intentional adulteration, and trade relations and geopolitical risk. Geopolitical conflict and degradation of international trade relations could prove

[8] Aitken M, Kleinrock M, Drug Shortages in the U.S. 2023, The Use of Medicines in the U.S., Spending and Usage Trends and Outlook to 2025, IQVIA Institute, p. 25, May 2021, found at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-use-of-medicines-in-the-us-2023/the-use-of-medicines-in-the-us-2023.pdf.

[9] Aitken M, Kleinrock M, Drug Shortages in the U.S. 2023, The Use of Medicines in the U.S., Spending and Usage Trends and Outlook to 2025, IQVIA Institute, p. 49, May 2021, found at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-use-of-medicines-in-the-us-2023/the-use-of-medicines-in-the-us-2023.pdf.

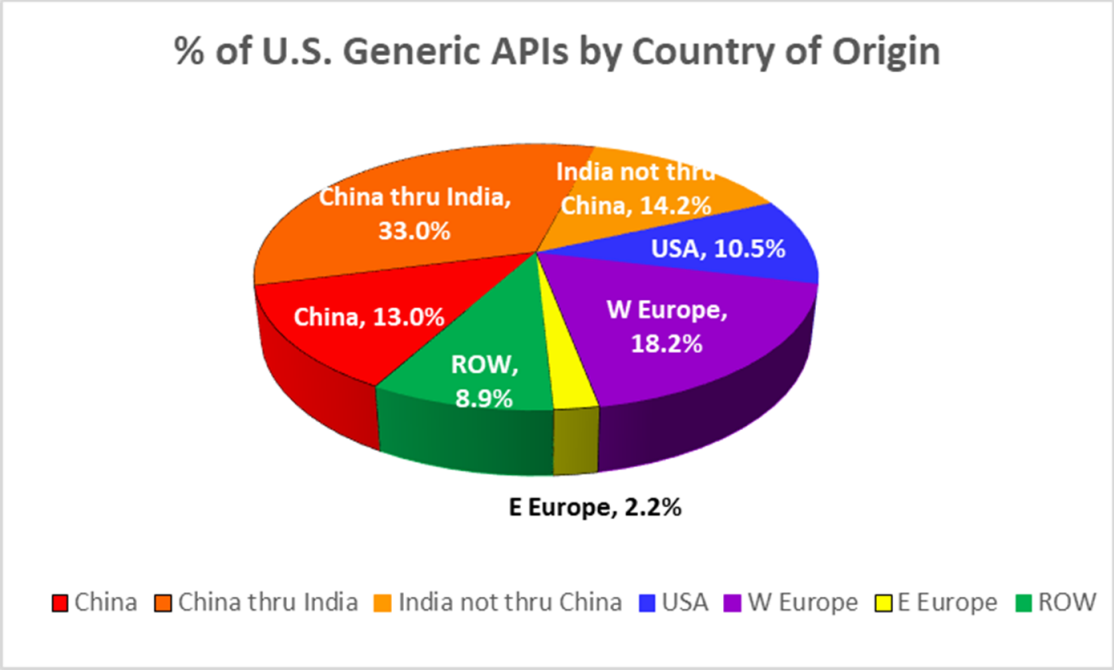
[10] Aitken M, Kleinrock M, Pritchett J, Drug Shortages in the U.S. 2023, A Closer Look at Volume and Price Dynamics, IQVIA Institute, p. 2, November 2023; found at: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/drug-shortages-in-the-us-2023.

catastrophic for the health and national security of all Americans including our military personnel. With drug shortages near an all-time high in the U.S., both the U.S. civilian population and military personnel are vulnerable to adverse health consequences from these critical drug shortages. Continued disruptions, either intentional or unintentional, in the upstream U.S. drug supply threaten the public health and national security of Americans.

Based on research at the Resilient Drug Supply Project (RDSP) using data from CGI Cortellis, FDA, and other sources, the following conditions in the upstream market create geopolitical vulnerability for the U.S.:

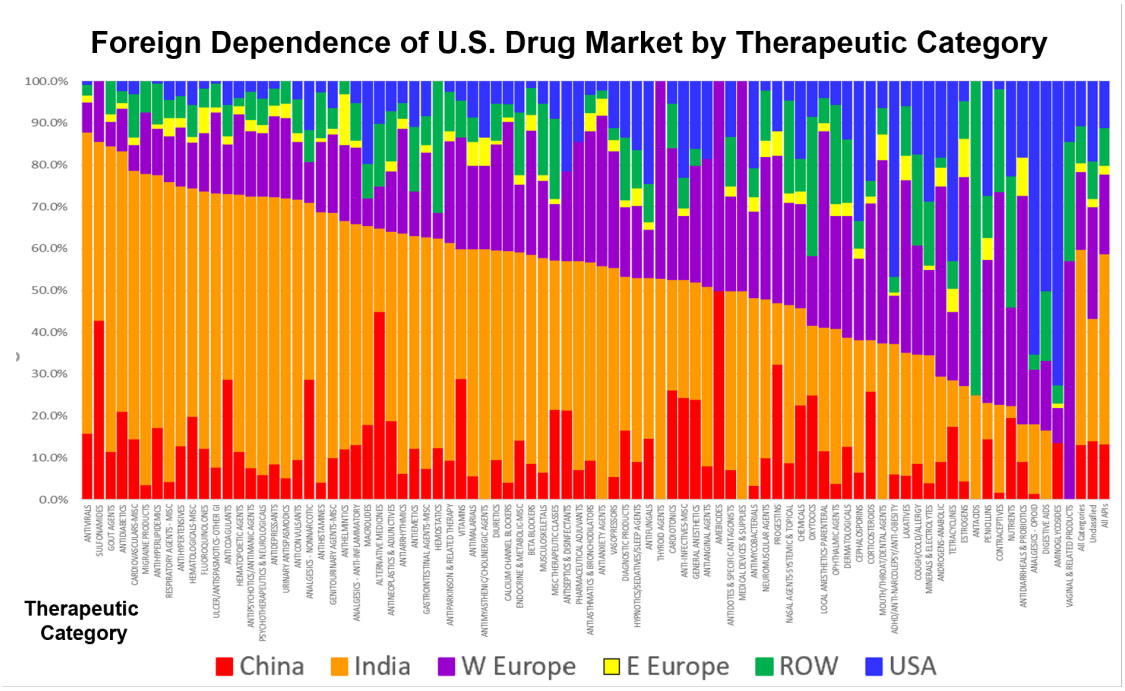
- The U.S. drug supply is heavily dependent on foreign sources with most generics coming from India and China and most patented brands coming from Europe.
- >60% of all U.S. daily drug doses have API or finished product from China or India.
- India is dependent upon China for about 70% of its API sources,
- India alone & India through China accounts for 47.2% of API facilities (Fig.1).
- China alone & China through India account for 46% of API facilities (Fig.1)..
- The U.S. accounts for only about 10.5% of the API facilities (Fig.1).
- Greater than 80% of the world's fermentation antibiotics are made in China.
- There are about 100 important APIs made only in China and nowhere else.
- There are about 229 important APIs made only in India and nowhere else.
- There are about 680 important APIs made only outside of the U.S.
- In the past decade, U.S. API facilities have dropped from 3,198 to 1,247 (-61%).
- In the past decade, India's API facilities have grown from 1,433 to 5,109 (254%).
- In the past decade, China's API facilities have grown from 962 to 1,494 (55%).
- In the past decade, Taiwan's API facilities have grown from 58 to 247 (326%).
- In the past decade, Israel's API facilities have grown from 108 to 250 (131%).
- The four countries with the fastest growing API capacity are geopolitical hot spots.
- Most therapeutic categories depend on India or China for >50% of their API facilities (Fig.2)..

Figure 1.



Source: Analysis by Resilient Drug Supply Project, University of Minnesota, based on data from CGI Cortellis and other sources, 2022.

Figure 2.



Source: Analysis by Resilient Drug Supply Project, University of Minnesota, based on data from CGI Cortellis and other sources, 2022.

Drug manufacturing has undergone a shift from in-house production to production through Contract Manufacturing Organizations (CMOs) and Contract Development & Manufacturing Organizations (CDMOs). Essentially the pharmaceutical manufacturer has become like the general contract for home builders—one firm coordinates all of the contributors who are building the house, but the general contractor does not actually 'make' the house. Also, it is not clear whether the FDA has the same degree of oversight for CMOs and CDMOs and their role in manufacturing drug products for the U.S. market.

Another shift in the drug manufacturing process for APIs and FDFs has been the move from U.S.-based facilities to facilities in Asian countries, especially India and China. Over the past two to three decades, many firms in the West looked to Asian countries for production of API and FDF because of lower cost of labor, lower cost of production, fewer environmental regulations, and economy of scale in production and other factors.[11] Asian countries usually have a 40% to 60% lower cost structure than Western nations when it comes to pharmaceutical production. As noted earlier, in just the last decade the number of U.S. API production facilities has decreased more than 60%. With strong cost reduction pressures, it will be difficult to move production of API and FDFs back to the West without substantial incentives.

The pharmaceutical market needs to move toward API production that has built-in redundancy of production sites. Dual sourcing, when possible, should be the minimum best practice with additional locations of production when the market is large enough to support them.

The U.S. and other countries should move toward regional markets with re-shoring and friend-shoring of redundant API production facilities. The U.S. can encourage some re-shoring of API production in the U.S., but it is also important to diversify the location of redundant API production facilities. For example, if two API facilities were built in Puerto Rico, a single hurricane could disable both of the redundant facilities. As a result of Hurricane Maria in 2017, a major share of the U.S. large volume parenteral solutions market was disrupted and hospitals throughout the U.S. had to find alternative products.[12]

The U.S. needs to have visibility into the market-wide upstream supply chain for API and FDF facilities and which products each one makes. This upstream drug supply map can then be used to target incentives to the products most needed and most likely to

[11] Bumpas J, Betsch E, Exploratory Study on Active Pharmaceutical Ingredient Manufacturing for Essential Medicines, Health, Nutrition and Population, The World Bank, September 2009, p.12.
[12] McGinley L, Hospitals scramble to avert saline shortage in wake of Puerto Rico disaster, Washington Post, Oct. 9, 2017, found at: https://www.washingtonpost.com/news/to-your-health/wp/2017/10/09/hospitals-scramble-to-avert-saline-shortage-in-wake-of-puerto-rico-disaster/.

experience drug shortages. Drug molecules with only one source of API production in the world are vulnerable, and especially if they are located in a country that is geopolitically sensitive. Also, even if there are two or three API production facilities, but they are located in the same country, there is more risk than if they are located in different countries.

Quality of Production Issues

The quality of drug products is of the utmost importance in the pharmaceutical market. The U.S. FDA has specific authorities and appropriations from the U.S. Congress with respect to the quality of production processes used by pharmaceutical manufacturers. Within the scope of their authorities, FDA has issued detailed guidelines for Good Manufacturing Practices that are to be voluntarily followed by pharmaceutical firms.

There have been concerns over the FDA's ability to assure quality with limited foreign inspection capabilities. Both the number of inspections done and the ability to engage in unannounced inspections, limit FDA's opportunity for meaningful inspections overseas. In recent years there have been a growing number of recalls and product withdrawals because of quality problems. Since 2015 companies have recalled products of more than ten drug molecules due to NDMA (or other potential carcinogen) contamination levels. FDA has also recalled batches of eye drops and baby formula because of bacterial contamination that led to patient harm and in some cases, deaths. While improved and increased frequency of inspections may be helpful in minimizing these quality issues, a broader approach to quality assurance is also needed.

In 1990, the U.S. FDA was a founding member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). There are now 13 countries who are regulatory members of the ICH who agree to participate and implement harmonized drug regulations. In addition to the United States, other countries participating as members of the ICH include Canada, Mexico, the European Union, Japan, China, and others. Notably, India is not a member of the ICH. Recall that India is the single largest producer of drug products for use in the United States, yet the country does not participate in the ICH.

Not only does India not harmonize with other countries on drug production and regulation, but the Indian regulatory scheme for pharmaceutical production is delegated to each of the 38 state entities within India. India's drug manufacturing and regulatory scheme is "a fragmented system spanning 38 drug regulators."[13] There is lack of coordination even within India. One observer noted that if one state finds a violation, the violation is not likely to be shared with other states or federal regulators.

[13] Kaul R, Govt plans common drugs standards for all state regulators, Hindustan Times, March 17, 2023, found at: https://www.hindustantimes.com/india-news/govt-plans-common-drugs-standards-for-all-state-regulators-101678990617259.html.

This situation needs to be addressed by the FDA, the U.S. Trade Representative, the Department of Commerce and other sources for exerting leverage on India to participate in the ICH for harmonization of drug regulation with the U.S. and other major world partners.

Emerging Trade Opportunities & Barriers

The U.S. needs like-minded trading partners to secure its drug supply chain. Re-shoring the manufacturing of both APIs and finished drug products can be part of the solution for a more resilient drug supply. However, it is not feasible for the United States to manufacture all, or even most, of its needed pharmaceuticals. Near-shoring to markets, such as Canada and Mexico or other places in the Americas, will allow for cost-effective production while affording improved geographic access and opportunities for strengthened trade partnerships. While drug firms in Mexico, and other countries in the Americas, have expressed interest in developing or increasing the production of APIs for export to the U.S., they would require significant policy support and subsidization to be competitive in the market with countries like China and India.

The U.S. should pursue trade partnerships with other countries in the Americas as alternative sources of pharmaceutical production. The COVID-19 pandemic has challenged global supply chains, in general, and, in particular, it has sensitized the United States to the heavy dependence it has on Asian countries and especially China and India. Currently, *U.S. policymakers are looking for alternative supply channels to decrease the U.S. dependence on China and India for critical and essential pharmaceuticals.* One solution is encouragement of re-shoring to the U.S. of pharmaceutical manufacturing for critical active pharmaceutical ingredients (API) and finished dose forms (FDF). In addition to increased U.S. production of pharmaceuticals, there is a need to develop geographically diverse supply chains that address environmental, economic, and geopolitical challenges.

Geographic diversity of supply sources is needed in the Americas. Mexico, Canada and other nearby countries can provide near-shoring of pharmaceutical production that can decrease the U.S. dependence on more distant Asian sources such as China or India. Near-shoring in Mexico, Canada or other countries in the Americas is a means to minimize over-concentration of production in Puerto Rico or the mainland of the United States.

Near-shoring can improve logistics and transportation. *Mexico, Canada and other nearby countries are geographically juxtaposed to the U.S. and offer more efficient shipping and logistical access.* For example, Mexico is strategically located at the southern edge of the United States where it shares a border with four states (i.e., Texas, New Mexico, Arizona and California). Mexico's proximity and physical border with the U.S. enable transportation and shipping routes by rail and road that are entirely

over land. This means that shipping of pharmaceuticals from Mexico can avoid more expensive and congested sea and air transport.

There may be a lower cost of production through near-shoring. *Mexico can produce pharmaceuticals at a cost that is 14.4% less than in the U.S.* By comparison, Canada can produce pharmaceuticals at a cost that is 4.6% less than the U.S. and in Italy, costs are about 1.9% less than in the U.S.[14]

Near-shoring can improve inspection access. Pharmaceutical production in Mexico would allow FDA to have improved access to manufacturing facilities for inspection and oversight. The FDA does have an office and staff based in Mexico, which would facilitate more frequent and efficient inspections for quality and Good Manufacturing Practices than can be achieved in Asian countries.

The COVID pandemic, however, precipitated some new trade issues with respect to pharmaceuticals. India, for example, imposed export curbs on 13 APIs and 13 drug product formulations.[15] These export bans were to ensure that India would have enough drug product to treat the Indian population. Under pressure India reversed the ban in one day. China imposed bans on masks and ventilators. Other countries instituted limited bans on exportation of drugs and medical supplies. Policy experts worried that if every country turned protectionist in the time of a pandemic, only producing countries would have supplies and others would be without needed drugs and medical supplies. One article recommended that "The world needs to change how it trades drugs."[16] The trade disputes were not over intellectual property rights, but rather access to exports of certain drug products used to treat pandemic-related conditions. China threatened to embargo trade of certain drugs which would have left the U.S. vulnerable or without those certain critical drug products.

One final trade issue with respect to prescription drugs is the importation of drugs from Canada under a program proposed by the State of Florida. On January 5, 2024, the FDA authorized Florida's drug importation program.[17] The Florida program is limited to providing drugs under certain state-run health programs through the Department of Children and Families, the Department of Corrections, and the Department of Health.

[14] PharmaBoardroom.com, Mexico: Healthcare & Life Sciences Review, Nov. 2015, p.39.
[15] Wallace D, India Curbs Exports Amid Coronavirus, Restricted Products, Include Paracetamol API and Formulations, Generics Bulletin, Mar 4, 2020.
[16] Tripathi S, The World Needs to Change How It Trades Drugs, Foreign Policy, April 21, 2020..
[17]

Prior to approval of the Florida plan, the FDA did not permit importation of prescription drugs from Canada although there were a few very specific exceptions. Upon hearing of the FDA approval of the Florida reimportation plan, the Canadian government took action to ban export of prescription drugs from Canada, if the export would leave Canadians without needed medications.

This FDA-Florida-Canada interaction over importation of prescription drugs from Canada at a low cost will need active intervention by the U.S. administration including the FDA, the U.S. Trade Representative, and the Department of Commerce, if it's going to work. Keep in mind that Florida has a population of 21.8 million while Canada's population is 38.5 million. A robust importation program by Florida could deplete a major portion of the drugs in the Canadian market--and Canada is not likely to let that happen.

Strategies to Minimize Geopolitical Risks & Other Vulnerabilities

Just as the U.S. would not rely on its enemy for bullets, neither should we rely on a major geopolitical rival for critical drugs to treat the U.S. population or military forces—the source of our drug supply is a matter of national security. The U.S. needs to have a strategic plan for drug supply with policies and incentives to ensure a secure and resilient supply of all essential and necessary drugs. Continuous work is needed to identify risks and secure the supply of key starting materials and API for critical pharmaceuticals. The U.S. needs improved quality inspection and enforcement to prevent unintentional drug quality problems from lack of voluntary compliance and inadequate regulatory oversight (e.g., India, China, or even at facilities in the U.S.). The U.S. needs intensified security and quality monitoring to prevent deliberate attacks and threats posed by drug production in politically adverse settings.

The U.S. needs to encourage more re-shoring, near-shoring and friend-shoring of API and finished drug production especially for critical drugs, increased transparency of drug production sourcing, and de-risking of the supply chain. The U.S. lacks a centralized system to effectively map, track, predict, and respond to drug shortages. The FDA itself reports difficulties monitoring the production, quality, and distribution of active pharmaceutical ingredients (APIs) in foreign countries, especially in locations such as China and India.

The upstream drug supply chain in the U.S. needs to be mapped in order to identify vulnerabilities, to prevent disruptions, and to prepare coordinated responses. There is a need for an international global system for addressing drug shortages and their causes so that preemptive action can be taken to prevent future drug shortages. Comprehensive information on drug supply and drug shortages is needed to provide awareness of vulnerabilities that is timely and transparent enough to predict and respond to drug shortages before the public faces real and significant consequences.