INTRODUCTION

The COVID-19 global pandemic has underscored the critical need for resilient and secure supply chains, particularly in the pharmaceutical industry. As the United States grapples with near-all-time high drug shortages and the vulnerability of its supply chain, it has become a national security imperative to address the overreliance on imports for active pharmaceutical ingredients (API) to the United States. Today, China is the sole source for about 20% of the API of our most vital medicines. More dangerously, China’s overwhelming global dominance of the key starting materials (KSM) required to produce these essential medicines cannot be readily substituted due to the current levels of market concentration: approximately 45% of KSM, a vital subcategory of API, are solely sourced from China, according to the API.

2 USP and Center for Analytics and Business Insight, Olin Business School at Washington Louis University, unpublished data image, October 13, 2023.
Innovation Center.\textsuperscript{3} To be sure, this level of import dependence on any single nation poses a serious risk to the nation’s general preparedness and resilience, and could become devastating in a crisis.

Highlighting the issues the United States faces: drug shortages in the nation’s healthcare system consistently affected approximately 300 medicines throughout 2023.\textsuperscript{4} Moreover, during most of 2023, many operational military units could not get allocation for primary ketamine injection, commonly used for sedation and analgesia during deployment operations.\textsuperscript{5} Upon further investigation, the primary reason these shortages happen is when market forces drive too much concentration or consolidation in the global marketplace; this often leads to lack of focus and investment in current good manufacturing practices and the exclusive focus on drug cost without much regard to supply chain resiliency and product quality.

This briefer is based on a retrospective and prospective assessment of this strategic risk, along with numerous inputs from industry, academic, and government experts and reports. It also identifies and recommends several specific and feasible actions that can be implemented immediately to address the risk. Additionally, this document calls on policymakers, business leaders, and national security professionals to recognize that the domestic medical supply chain’s reliance on China is equally as threatening as our reliance on China for critical minerals and rare metals for the production of semiconductors, electronics, renewable energy hardware, supercomputers, and our most advanced weapon systems.

\textbf{WHY SHOULD THE UNITED STATES STOCKPILE KEY PHARMACEUTICAL INGREDIENTS?}

\begin{itemize}
\item Critical commodity which could undermine the nation’s healthcare system and national defense mobilization and sustainment capabilities during geopolitical tensions.
\item Depending on the nation’s pacing military threat and largest economic competitor for these materials is a significant security threat.
\item Key Starting Materials (KSM) and Active Pharmaceutical Ingredients (API) stockpiles in the US would provide strategic flexibility and agility and can be stored for many more years than finished pharmaceutical products. They also can cover a broad spectrum of finished products further up the supply chain.
\item The US government has a long history of stockpiling materials deemed essential for national security.
\item Pharmaceutical ingredient stockpiles can provide a solid foundation to stabilize the economy, advance the continuity of high-quality patient care and long-term health outcomes, and provide essential predictability to patients, government and first responder actors, and the pharmaceutical and healthcare industries.
\end{itemize}

Notably, this issue is already garnering policy-maker attention. The risks of pharmaceutical supply chain dependence were underscored in the US House Select Committee on China Report dated 12 Dec 2023, titled “\textit{Reset, Prevent, Build: A Strategy to Win America’s Economic Competition with the Chinese Communist Party}.”\textsuperscript{6} Congress also showed its attention to addressing import-dependence risks when it passed the 2022 CHIPS and Science Act.

\begin{itemize}
\item \textsuperscript{3} Ibid.
\item \textsuperscript{4} Erin Fox, “National Drug Shortages Active Shortages by Quarter – 10 Year Trend,” \textit{University of Utah Drug Information Service}.
\item \textsuperscript{5} Victor A. Suarez, author’s first-hand experience with customer and stakeholder inquiries, June 2023.
\item \textsuperscript{6} The U.S. House of Representatives, \textit{House Select Committee Report on the CCP}, December 12, 2023.
\end{itemize}
which made a $53B investment for manufacturing, research, and development, and workforce growth to revitalize the domestic semiconductor industry and reduce domestic reliance on overseas manufacturers. Within a year, this act incentivized the industry to pledge over $166B in investments to bolster domestic semiconductor manufacturing, highlighting the significance that initial priming and commitment from the government can have in boosting private markets to infuse additional capital.

One difference between overseas reliance on essential medicines and semiconductors is that, should there be a severe drug shortage or an embargo due to geopolitical reasons, people will unnecessarily die due to not having their essential medicines, and health systems will fail to deliver quality care. The risks of the status quo could be even more pronounced if these first-order effects occur at a time when systems are already strained by epidemics or pandemics, conflict, or other conditions. This briefer will describe the fragile state of domestic United States generic pharmaceutical manufacturing, address why the pharmaceutical supply chain is a major national security issue, and propose immediate, mid-term, and long-term solutions to eliminate these critical strategic risks.

CURRENT STATE OF DOMESTIC PHARMACEUTICAL MANUFACTURING

A study released in late 2022 by the API Innovation Center looked into the United States generic pharmaceutical manufacturing plant capacity and found that despite an approximate 10% growth in demand for medicines from 2016-2021, “these sites are producing at just half of their production capacity, with an aggregate excess capacity of nearly 50%.” This average, being 30% below the U.S. total industry capacity utilization rate average of approximately 80%, means that unlike many other commodity markets in the U.S., the generic pharmaceutical industry’s underutilization places domestic drug manufacturers at significant risk of additional plant closures, further market concentration, and acquisition by foreign entities. It also perversely incentivizes more off-shore buying activities, generally in countries with access to cheap labor which often struggle to produce consistently high-quality medicines, as meticulously documented by Rosemary Gibson and Janardan Prasad Singh in their seminal book *China Rx.*

Most group-purchasing, pharmacy benefit management, and rebate schemes with exclusively contracted member hospitals have further complicated the pharmaceutical market and its underlying economics. Despite being well-intentioned, antitrust practices in what is essentially an oligopoly have pushed the cost of many generic medicines so low and hence


off-shore that domestic manufacturers cannot financially justify producing these medicines, let alone invest in advanced manufacturing technologies to improve and sustain production quality.\(^\text{10}\)

Moreover, this incentive to drive the lowest possible costs for generics has led to massive displacement of drug manufacturing to India and China over the past three decades, creating a perfect storm for any dysfunctional marketplace, which includes opaqueness in supply origins, product quality issues, and lack of pricing trade-offs. In both these countries, there are large backlogs in Food and Drug Administration (FDA) inspections and many documented cases of poor manufacturing controls. This unfortunately provides an enormous incentive to grow global market share in these countries due to less regulatory and environmental oversight, cheap manufacturing and sourcing of KSM and API, and underinvestment in quality manufacturing technologies, processes, facilities, and staffing. These combined factors place the strategic risk of reliably sustaining pharmaceuticals in America squarely upstream in the supply chain. This multicomponent downward spiraling of the above factors will lead to more drug shortages, mainly as a byproduct resulting from quality manufacturing issues driving plant closures—an expected outcome of less frequent and episodic regulatory plant inspections.\(^\text{11}\)

As a result of this unsavory mixture of flawed market forces and perverse incentives making quality more challenging to achieve, the U.S. healthcare system is currently dealing with a near all-time high drug shortage, consistently affecting approximately 300 medicines throughout 2023.\(^\text{12}\) These shortages not only adversely impact patient care but present life-threatening risks to many cancer and chronic disease-afflicted patients. These shortages also adversely affect our tactical military operations, foreshadowing a strategic national security vulnerability during a crisis or war.

### NATIONAL SECURITY IMPLICATIONS AND GENERAL RECOMMENDATIONS

One of the most critical national security lessons from U.S. experiences in major wars is the importance of having domestically vital manufacturing industries and vertically integrated supply chains before mobilizing at scale. In Arthur Herman’s 2012 New York Times best-selling book, “Freedom’s Forge: How American Business Produced Victory in World War II,”\(^\text{13}\) Herman describes how critical America’s steel, chemical, and automotive manufacturing plants were - producing thousands of tanks, airplanes, ships, and explosives - in eventually defeating the Nazis and imperial Japan. Similarly, during World War II, the U.S. pharmaceutical industry also dramatically expanded in response to the need for critical medicines such as penicillin, sulfa drugs, and other life-saving medical supplies.\(^\text{14}\)

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10 Numerous interviews with industry and government experts, October 2023 through January 2024.


12 Erin Fox, “National Drug Shortages Active Shortages by Quarter – 10 Year Trend,” University of Utah Drug Information Service.


The United States can and should take action now so that any potential disruption of KSM and API from a sole source supplier—for example, in case China ceases exports due to tensions over Taiwan—would not result in the collapse of our health system. A minimal goal should be preventing a significant catastrophic disruption worse than the 2020-2023 COVID-19 pandemic.

Stockpiling is one approach the United States has commonly taken to mitigate such risks. In 1977, the Strategic Petroleum Reserve (SPR) received its first crude oil deliveries and was created to reduce supply disruptions and avoid the devastating effect of oil embargo during geopolitical tensions. In 2020, in response to the COVID-19 pandemic, the US government funded the construction of a pharmaceutical equivalent to the SPR, called the Strategic Active Pharmaceutical Ingredient Reserve (SAPIR). However, instead of financing it to maintain nearly two years’ worth of supply and incentivizing private industry to incorporate it into a means to wean off reliance on overseas supply, it currently sits at approximately 1% of its capacity.

The United States should begin filling the near-empty SAPIR stockpile warehouse with essential API and KSM this year. This action would be no less necessary than the United States addressing the need for petroleum reserves starting in 1910 after the US Navy began converting its ships from coal to oil as fuel. Establishing strategic reserves for critical API and KSM would enable the US government to remove the potential significant leverage that China could exercise over the United States if it so chose—and help create paths to reducing the risk that such an import dependence might create with other nations in the future. A consistent national security plan would complement actions the US government has already taken to address other vulnerable areas, like cybersecurity, as it would ensure that, despite an embargo of key API and KSM, the United States could rapidly release essential materials and ingredients to domestic drug manufacturers and ensure production continuity and quality ingredients of finished products. Furthermore, stockpiling API makes sense as typically KSM and API have a three to four times longer shelf-life than finished drug products.

An additional and often overlooked aspect of having a national strategic KSM and API reserve is to ensure our military can rapidly build up their medical supply stocks as quickly as possible. In addition to the deterrence value of strong preparedness, this would help meet the need that the Department of Defense’s demand for these items in case of war would surge significantly more (on a per person basis) than any demand from the civilian healthcare system. This proposed national KSM and API “safety stock” capability would enable an industrial base that can mobilize effectively during a crisis or war and is complementary to a series of foundational industrial capabilities and investments that can ultimately help deter attacks.

During most of 2023, many operational military units could not get allocation for primary ketamine injection, commonly used for sedation and analgesia during deployment operations. Upon further investigation, the primary reason these shortages happen is when too much concentration or consolidation

16 Interviews with key experts to remain anonymous.
17 Naval Petroleum and Oil Shale Reserves, “Ninety Years Ensuring the National Security,” accessed February 7, 2024.
18 Victor A. Suarez, author’s first-hand experience with customer and stakeholder inquiries, June 2023.
occurs in the global marketplace. This, in turn, leads to an oligopoly when often only one, two, or three global manufacturers remain for a critical drug. This typically occurs when domestic manufacturers begin closing plants or cease making select medicines when foreign competitors in places like China and India offer rock-bottom prices, sometimes with government subsidies and often because of much cheaper labor, fewer environmental restrictions, and underinvestment in quality manufacturing processes, equipment, and facilities.

And, if there is a quality issue or a shortage in API or key material due to manufacturing quality delays when one-third or half of the world’s supply is unavailable, a major drug shortage ensues, thus eroding patient care and military readiness. Typical status quo actions to address this include implementing minor, incremental improvements (such as requiring manufacturers, distributors, and hospitals to create buffer stockpiles of finished products, or for generic-drug manufacturers in other nations to invest in higher-quality manufacturing technologies) and desperate efforts to import non-FDA-approved medicines. However, to effectively address such a potential shortfall, we ought to explore, debate, and finally take action on feasible solutions which may better address the root causes of this strategic vulnerability in the generic pharmaceutical industry.

Finally, on November 27, 2023, the Department of Defense (DOD) sent its interim Pharmaceutical Supply Chain Risk Assessment to the House and Senate Armed Services Committees, as mandated in the FY23 National Defense Authorization Act (NDAA), Section 860. A significant finding was that 54% of the national drug codes (NDCs) sourced by the DOD came from countries not compliant with the Trade Agreement Act (TAA) and were derived from China, India, or of unknown origin. Not only does this recent finding present a clear and present danger for national security, it also compels us to explore other legal and trade policies which erode rather than strengthen our economic and health security, such as those addressed in the controversial Acetris Health, LLC v. United States case from February 2020. In this case, the U.S. Court of Appeals for the Federal Circuit overruled a long-standing precedent regarding the origin of a drug by ruling that a drug could be considered to be “manufactured” in the U.S. even if its API and all of its components were derived from TAA-banned countries, such as China and India. This loophole exacerbates national security and known drug quality risks. As such, this case should be brought before the Supreme Court or remedied with a more precise interpretation by Congress of what it means to have a pharmaceutical substantially made in the United States.

SPECIFIC IMMEDIATE, MID-TERM AND LONG-TERM SOLUTIONS AND RECOMMENDATIONS

As we migrate from understanding the background of our drug supply chain vulnerabilities and the national security implications of overrelying on foreign derived KSM and API, this briefer proposes the following specific immediate, mid-term, and long-term solutions and recommendations.

19 API Innovation Center, Addressing the Acetris “Loophole,” Aug 2023
IMMEDIATE SOLUTIONS AND RECOMMENDATIONS (YEARS 1–2)

1. The U.S. government should commit to sustaining the Department of Health and Human Services (HHS) Administration of Strategic Preparedness & Response (ASPR) by purchasing at least an 18-month supply of essential KSM and API and stockpiling them in the already-built SAPIR facility under a dynamic life-cycle managed stability and stock rotation program (industrial conversion). An 18-month supply is estimated to cost in the tens of millions of dollars—a tiny fraction of the security return on investment. It is calculated by some leading industry experts to be able to be completed in less than one year.\(^\text{20}\)

2. ASPR, in partnership with the newly created HHS Supply Chain Resilience and Shortage Coordinator,\(^\text{21}\) should coordinate and prioritize purchases for specific items with the DOD and the FDA. ASPR should also take the lead on collecting the diverse and sometimes diverging inputs from various non-governmental and industrial organizations already monitoring this vulnerability in deciding which purchases to prioritize.\(^\text{22}\)

3. Operationalize and sustain staffing of the SAPIR facility and at least quarterly test its ability to release key materials to address temporary shortfalls in domestic supply and measure progress against domestic pharmaceutical manufacturing capacity utilization rates as surveyed and measured by leading industrial manufacturing trade organizations.

4. Government and private healthcare systems should work together to ensure all purchased KSM and API for the SAPIR meet or exceed US Pharmacopeia (USP) and FDA quality standards by implementing independent third-party testing and supplier audits for the chemical quality attributes of these materials. The FDA should embrace more independent quality testing of medicines and coordinate efforts with the European Medicines Agency (EMA) and the European Union’s Official Control Medicines Laboratories for allied and international partner harmonization of quality product standards to expand the scope and reach for detecting poor quality, adulterated, and fraudulent medicines. They should also ensure that all advanced purchase agreements for materials include requirements for quality audits and testing for authenticity, purity, contaminants, and carcinogens within USP/FDA standards where applicable.

5. The Department of Commerce’s Economic Development Administration (EDA) should revitalize the Federal Loan Guarantees for Innovation Technologies in Manufacturing (ITM) program for the domestic generic pharmaceutical industry. ITM could provide:

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20 Author interviews with industry experts at the C–Suite level.

21 Biden–Harris Administration Announces Actions to Bolster Medical Supply Chain | HHS.gov, accessed 12 February 2024.

22 These NGOs include the American Society of Health-System Pharmacists (ASHP), the API Innovation Center (APIIC), the Association for Accessible Medicines (AAM), the End Drug Shortage Alliance (EDSA), the American Hospital Association (AHA), Physicians Against Drug Shortages (PADS), the Duke-Margolis ReVAMP Drug Supply Chain Consortium, Pharmaceutical Research, and Manufacturers of America (PhRMA), and the United States Pharmacopeia (USP).
- Grants or loans to established U.S.-based pharmaceutical companies that possess FDA-approved medicines that are currently manufactured in Trade Agreement Act (TAA) non-compliant countries such as China or India to technically transfer current Good Manufacturing Practice (cGMP) processes and sources of supply of these medicines to US manufacturing plants.

- Priority for loans for any medication (generic small molecule or biologics) on the FDA essential medicines list, with the highest priority being medicines, API, and KSM which are currently solely sourced from China or any other single country.

6. The U.S. government should create and fund HHS/ASPR to host a unique grant program for domestic generic drug manufacturers for FDA-approved medicines that are exclusively made in China or any other single nation but are considered essential for life-threatening (oncology medicines), chronic (cardiac/metabolic/autoimmune), neurological, and infectious diseases (beta-lactams), which could be technically transferred to a US manufacturing plant. Approval considerations should include whether the recipient companies are willing to cost share, whether the medicine is sole-source manufactured in TAA non-compliant nations, the severity of the disease treated by the medications, whether there are alternative medicines available, and if the medicine is essential for national defense (DOD essential medicine list) or is stockpiled in the US Strategic National Stockpile.

7. The API Innovation Center recommends that Congress closes the Acetris ‘loophole’ by revising the U.S.-made end product definition and clarifying that the definition of “manufacture” requires meeting the “substantial transformation” standard to encourage the industry to work toward manufacturing API and other critical components of pharmaceuticals in the U.S.

The US House Select Committee on China Report issued in December 2023 also recommends that Congress consider the following near-term actions:

- Require the FDA to develop an expanded list of key pharmaceutical products widely used in the U.S. and maintain a database to track their supply chain.

- Authorize the U.S. Trade Representative to negotiate trade agreements to reduce U.S. dependencies on People’s Republic of China medical and pharmaceutical goods.

- Direct a Buy American program for federal entities that purchase pharmaceuticals and medical devices.

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23 Active Pharmaceutical Ingredient Innovation Center, accessed 7 February 2024

24 House Select Committee on the Strategic Competition Between the United States and the Chinese Communist Party, accessed 12 Feb 2024
MID-TERM SOLUTIONS AND RECOMMENDATIONS (YEARS 1–5)

8. Once the SAPIR stockpile program has been initiated, the U.S. government should direct ASPR’s Industrial Base Management & Supply Chain (IBMSC) Program Office to pivot to a parallel project to identify and incentivize capable domestic manufacturers to produce KSM and API for every sole source material currently produced in China with a target to replace the initial purchased stock within five years using a dynamic domestic industrial materials conversion and life cycle management program.

9. HHS/ASPR should ensure the initially acquired products sold or delivered to the SAPIR facility are contracted in competitive, long-term advanced purchase agreements. Preference should be given to domestic manufacturers specifically focused on API and KSM manufacturing for sales to the SAPIR simultaneously and until the United States has 18 months’ worth of stock based on net imports of foreign-sourced API and KSM. Incrementally shift from an acquisition-focused program from overseas sources to domestically produced sources over a period of two to five years or until a dynamic domestic product conversion program can be achieved.

10. The SAPIR operator should map and match the API and KSM to domestic drug product manufacturers and specific drugs that are in perpetual short supply to create an enduring marketplace of domestic long-term buyers and sellers in a transparent market-driven economy free from oligopolistic and predatory practices as done by some of the major Group Purchase Organizations and Pharmacy Benefit Managers.

11. Once the sole source API and KSM have been addressed as described in recommendations 1-4, transition to domestic or near-shore manufacturing for those API and KSM for which there may be only 2 or 3 suppliers globally or are aligned to drugs that have high HHI (Herfindahl-Hirschman Index, a standard index measurement of market concentration).

12. The U.S. government should find ways to incentivize the domestic manufacturing of medicines and their precursor chemicals (including KSM, API, and raw materials) and reward health systems and insurers for domestically sourcing these items. This may necessitate closing the Acetris loophole.

13. All federal agencies that have health systems (DOD, Department of Veterans Affairs, HHS) or have a significant role in reimbursements for pharmaceuticals (Centers for Medicare & Medicaid Services) should be required to adhere to the intent of the Berry Amendment via executive order which was enacted in 1941 to promote the purchase of certain US goods for national security and domestic trade purposes.

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27 International Trade Administration, “Berry Amendment”, March 1, 2024.
LONG-TERM SOLUTIONS AND RECOMMENDATIONS (YEARS 6-10)

14. Within ten years, ensure the SAPIR facility can stockpile all API and KSM for the essential medicines in the United States, as compiled by the US FDA, and adjust stock levels and rotations based on the monitoring of HHI for each essential drug and their likelihood to face a shortage as predicted by tools such as USP’s Medicine Supply Map.

15. ASPR’s Office of Industrial Base Management and Supply Chain (IBMSC) should measure and evaluate program success by developing well-designed metrics such as domestic manufacturing plant utilization capacity, drug shortages, regulatory quality findings, and HHI assessments for each essential drug. These metrics should be tested annually in state, regional, and national tabletop exercises based on real-world emergency mobilization scenarios for national defense and pandemic response.

END STATE

The U.S. has a domestic generic pharmaceutical manufacturing industry utilized at over 75% capacity within five years and can produce high-quality and reliable medicines that do not depend on China for the sole source of KSM and API within two years by operationalizing and stocking the SAPIR facility. The end state should also include a domestic manufacturing base that can maintain drug shortages below 100 drugs within five years and 50 drugs within ten years that is highly transparent and operates like other non predatory free-market commodity sectors.

At this sustained end state, the industry would not be beholden to oligopolistic organizations that erode the reliability and quality of supply, preventing manufacturers from investing in advanced and continuous manufacturing technologies or introducing innovative and disruptive technologies in the spirit of continuous product and process improvement. Finally, China would no longer be able to leverage an embargo of essential and sole-sourced pharmaceutical KSM and API during periods of tension in the United States-China relationship, and the domestic pharmaceutical industry would competitively and fairly operate within a healthy, transparent, high-quality, and ever-improving marketplace.

CONCLUSION

Correcting America’s overreliance on China for essential medicines and their upstream API and KSM is not only a matter of economic stability and critical national security purposes but also important because patients ultimately require these life-saving medicines. The recommended immediate, mid-term, and long-term solutions can begin to be implemented now. As recommended in this briefer, these proposed actions should be discussed, debated, modified, and implemented by policymakers, elected officials, government agencies, and private industry to ensure the pharmaceutical supply chain’s resilience, quality, and security. By diversifying suppliers, domestically producing critical materials, and fostering collaboration with like-minded allies and partners committed to quality

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and reliable medicines, the United States can mitigate the risks associated with its current overreliance on China (or any other single nation) within the first year of taking action.

The good news is that this is a fixable strategic problem. Yet it will take bold leadership to disrupt the status quo and dynamic efforts in an election year to achieve bipartisan, whole-of-government, and cross-industrial support to make this happen. It is time to rise above the powerful inertia of admiring the problem and begin to take action in 2024 to reverse the trajectory of this strategic vulnerability and rebuild the domestic pharmaceutical industry throughout the entire supply chain. This can be another example of how the United States can lead in achieving a common goal with its allies, its partners, and its patients.

ABOUT THE AUTHOR

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