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COMMENTARY

The U.S. medicine chest: Understanding the U.S. pharmaceutical supply chain and the role of the pharmacist

Ryan C. Costantino*

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ABSTRACT

The U.S. capacity to manufacture key essential medications has diminished. The U.S. pharmaceutical supply chain (USPSC) has diversified and now relies on international sources of active pharmaceutical ingredients and finished drug products (FDPs). Despite years of effort raising concerns about the USPSC, pharmacists and pharmacy technicians continue to spend a substantial amount of time and energy responding to, and mitigating the impact of, medication shortages, drug recalls, and the adverse outcomes related to low-quality medications. The extent of U.S. reliance on foreign sources of medications is largely unknown. Pharmacists do not have a reliable way to determine the country of origin (i.e., source), capacity, or geographic location of pharmaceutical manufacturers, limiting our ability to anticipate challenges or mitigate risks to our Nation's drug supply. The U.S. Food and Drug Administration's task of regulating quality and safety is challenging and will likely require additional safeguards and resources. In addition to pharmacists' engagement, solutions will likely need to leverage a mix of policy, economic incentives, and expanded objective surveillance testing. The U.S. pharmaceutical supply chain is complex, global, and goes beyond FDPs. The 2020 American Pharmacists Association House of Delegates has rightly asserted that "The quality and safety of pharmaceutical and other medical products and the global pharmaceutical and medical product supply chain are essential to the United States national security and public health." Pharmacy professionals on the front line engage with patients, identify medication-related issues, and engage in drug-procurement decisions. Pharmacists are essential to our nation's overall health and must be engaged in the development and implementation of strategies to safeguard the USPSC.

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The United States is largely dependent on foreign sources of medication

The United States no longer manufactures a number of life-saving essential medications.[1] Early warning signs of our dependency on foreign manufacturers include the 2001 anthrax attacks during which the U.S. government purchased large quantities of doxycycline from foreign sources and the closing of the last penicillin fermentation plant in 2004, largely driven out of business by global market forces.[1,2] Over the past decades, the U.S. pharmaceutical supply chain (USPSC) has increasingly relied on international sources for pharmaceuticals and pharmacists continue to dedicate a sizable amount of energy responding to, and mitigating the impact of, medication shortages, drug recalls, and the adverse outcomes of low-quality medications.[3,4] Concerns related to these topics have been highlighted in previous publications over the past decade yet continue to persist and may even be worsening in 2020.[5,6] These issues may be symptoms of a larger problem related to the dissolution of our domestic drug manufacturing industry and shortcomings in our regulatory framework, impairing our ability to ensure the availability, quality, and safety of U.S. medicines.[7,8]

U.S. regulatory framework

The U.S. Food and Drug Administration (FDA) provides definitions for several key terms that are helpful to understand

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* **Correspondence:** Ryan C. Costantino, PharmD, MS, BCPS, BCGP, Branch Chief, Data Innovation, Enterprise Intelligence and Data Solutions, Defense Health Agency, 3515 S. General McMullen Dr., Bldg. 1, San Antonio, TX 78226.
E-mail address: ryan.c.costantino.mil@mail.mil (R.C. Costantino).

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Key Points

Background:

- The extent of our reliance on foreign sources of medications is largely unknown.
- Ensuring the quality and safety of medications is essential to maintain public confidence and medication adherence and prevent adverse outcomes.

Findings:

- Given the increased media attention around this issue, pharmacy professionals might anticipate that the public may start seeking answers regarding the source or availability of their medication.
- Pharmacists are uniquely qualified to lead our Nation's effort to safeguard the U.S. pharmaceutical supply chain through advocacy, education, and engagement.

the USPSC. Raw materials, both organic and inorganic chemicals, are the building blocks used to manufacture active pharmaceutical ingredients (APIs) and inactive ingredients that together make up a finished drug product (FDP).[9] This FDP is what pharmacists often think of when dispensing a medication. It is estimated that up to 90% of the raw materials and APIs needed to produce an FDP come from China and other countries such as India.[7,8,10,11] In 2019, FDA reported that most API facilities (72%) and FDP facilities (53%) were located outside of the United States.[12] It is important to note that FDA does not track or inspect the raw ingredients further upstream (Figure 1).[3] Furthermore, the data provided by FDA usually only capture the organization that paid the registration fee to FDA (i.e., Generic Drug User Fee Amendments fee), potentially concealing the true location of manufacturers. Pharmacists are left with little insight regarding the quantity or volume of each drug produced at various facilities given that pharmaceutical companies often consider the information a trade secret.[3] The most conservative statement at this time would be that the extent of our reliance on foreign sources of medications is largely unknown. This is a cause for concern because without a reliable way to determine the country of origin (i.e., source), capacity, or geographic location of pharmaceutical manufacturers, pharmacists are unable to anticipate challenges or mitigate risks to the USPSC.

Medication quality and safety

In addition to the source of our medications, ensuring their quality and safety is essential to maintain public confidence, medication adherence, and avoid adverse outcomes.[13] Unfortunate events such as the 2008 heparin adulteration, 2018 angiotensin II receptor blocker (ARB) recalls, and the 2020 ranitidine removal request highlight that despite FDA's best efforts, regulating pharmaceutical products is complex.[14-16] In the case of the heparin and ARB recalls, the root cause was contamination or poor manufacturing of APIs. In the case of ranitidine, the issue was likely related to the unstable chemical properties of the drug molecule, which result in the generation of a known carcinogen during storage or in vivo.[17] FDA does require analytical tests and samples before new drugs are approved. FDA also conducts postmarket surveillance testing and inspections of manufacturing facilities to assess compliance with standards that may catch some of these issues. Domestic facilities can be inspected with no advance warnings, whereas international inspections are almost always announced in advance.[12] This raises the question as to whether domestic manufacturers are held to a different standard compared with international manufacturers. Owing to coronavirus disease, FDA has suspended foreign inspections and scaled back domestic inspections limiting the utility of this method of oversight.[18] In response, FDA is exploring new approaches to regulatory oversight such as a quality metrics program.[19]

Economic factors

Economic incentives may also have an impact on compliance with FDA regulations.[20-22] In the United States, companies that sell brand name drugs receive patent protection for 20 years after their original filing, affording them an opportunity to recoup their investment as a reward for their innovation. Because a brand name drug under patent protection has no competitor, companies have an incentive to maintain quality control to preserve the positive brand identity of their products. The primary economic incentive for generic manufacturers involves being the first generic drug applicant to submit a complete generic drug application. If approved, the applicant's generic drug may receive a 180-day exclusivity. It is to be noted that this patent exclusivity is far shorter in duration than the one that brand name companies receive. Although it still results in financial incentives for any company that receives it, it often requires generic manufacturers to operate on smaller margins to remain competitive, which may disincentivize spending on quality control. In the case of United States vs. Ranbaxy USA, Inc, the company was found guilty of submitting false and misleading information to FDA and forced to pay a fine. Over several years, Ranbaxy USA committed several violations, including adulteration, and failure to maintain records and meet Current Good Manufacturing Practice (cGMP) regulations. It is a great example of how these market forces play out in the real world, and raises the question as to whether FDA's current approach to regulation, which is largely based on trust, is still viable in today's globalized pharmaceutical marketplace.[23] One solution may be to expand FDA's ongoing chemical analysis of medications. Another might be to introduce independent objective pharmaceutical analysis (OPA) that could provide ongoing surveillance of our drug supply, and test for dissolution as well as ingredients, strength, and impurities. This is particularly important with extended- or sustained-release products owing to limitations of bioequivalence requirements.[24,25] To be clear, generic drugs are not inherently inferior to brand name medications, but they do receive different economic incentives, which can influence corporate behavior. It is estimated that 90% of Americans benefit from generic medications, thanks to the groundbreaking Hatch-Waxman Act, which reduced barriers to accessing medications worldwide.[26] Most medications, brand and generic, are of high quality, and no data have demonstrated a correlation

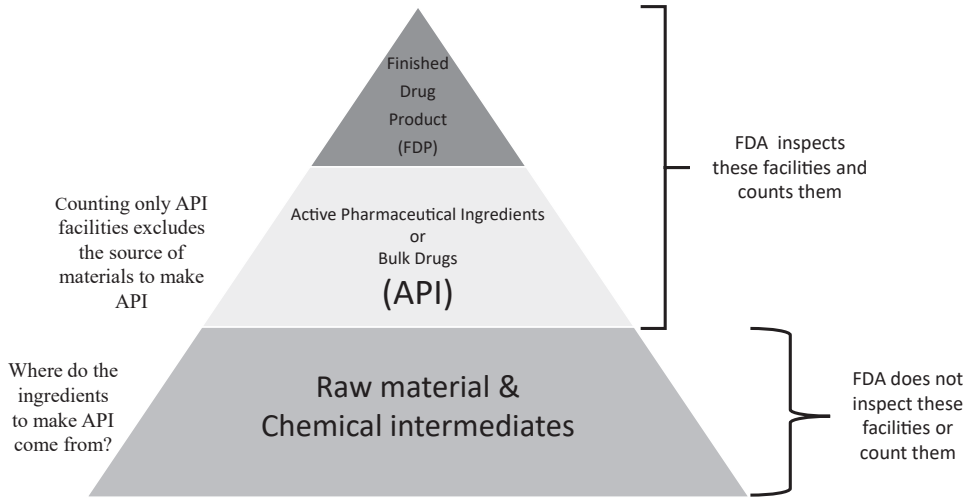

Figure 1. Medication components. Abbreviations used: API, active pharmaceutical ingredients; FDA, Food and Drug Administration; FDP, finished drug product.

between drug cost and quality, which highlights the need for pharmacists to be involved in pharmaceutical purchasing and logistics.

Regulatory challenges

Regulatory changes that improve transparency and quality management will likely have a positive impact but may present challenges. Increased transparency may highlight our dependency on foreign sources of medication. If patients, organizations, or the government start to demand "American-made" medications, a shortage could arise in the short run given the lack of domestic manufacturing capacity. It's unclear how the USPSC would respond in the long run. Increased OPA could identify new quality or safety issues. Regulators such as FDA may face a "Regulator's dilemma" where it has to make decisions about keeping low-quality medications on the market or risk inducing a drug shortage. A research letter published in *Circulation* related to the 2018 valsartan recall highlights the challenge our health system faces addressing these supply chain issues.[27] Jackevicius et al.[27] found that although most patients taking a recalled valsartan product switched to another antihypertensive drug, approximately 10% of the patients did not refill an alternative medication. They also reported a small but statistically significant increase in the rate of hypertension-related emergency department visits, which may be associated with the recall (from 0.11% to 0.17%; $P = 0.02$).

As health care shifts to a value-based model it is important to remember that value is a function of quality over cost:

$$Value = \frac{Quality\ (Efficacy\ and\ Safety)}{Cost\ (Direct\ and\ Indirect)}$$

As organizations hammer down on drug spending, there can be pressure to buy the cheapest medication available. However, if a medication is not as effective or causes adverse reactions that result in hospitalizations is it really providing value for the cost?[28] Pharmacists, along with regulators, will need to be engaged to advise patients, prescribers, and government leaders on the best solutions to address medication shortages, recalls, and other issues that may arise.

Laws and legislation

Acetris Health, LLC, vs. United States highlights the legal challenges of regulating the USPSC.[29] The case centers around the Trade Agreements Act (TAA), a piece of legislation often used to ensure that U.S. government organizations (e.g., Department of Defense [DoD] and Department of Veterans Affairs [VA]) procure medications that are U.S.-made.[30] The court ruled that a medication manufactured in the United States was TAA-compliant even if the API came from a non-—TAA-compliant country, which in this case was India. The court's ruling now only requires that an FDP be manufactured in the United States for the medication to be considered U.S.-made. This arguably lowers the standard or, at minimum, complicates the assessment of what is U.S.-made. Medicare and Medicaid programs are usually exempt from TAA requirements for medications, given that these programs, run by Centers for Medicare & Medicaid Services, reimburse for medications but do not physically purchase them. Requiring these programs or their funds to follow TAA would add leverage for other federal programs that purchase medications (e.g., DoD and VA) but may complicate or affect patients' access to medication at pharmacies that serve the Medicare/Medicaid population.

To address policy, regulatory, and legal gaps, health professionals and organizations have proposed strategies to improve the availability, quality, and safety of pharmaceuticals dispensed in the United States. The 2020 American Pharmacists Association House of Delegates (APhA HOD) recently adopted a series of policies aimed at protecting pharmaceuticals as a strategic asset.[31] The President recently signed an executive order titled "Ensuring Essential Medicines, Medical Countermeasures, and Critical Inputs Are Made in the United States."[32] Members of the U.S. Senate and House of Representatives have also introduced legislation that would have an impact on the USPSC if passed (Table 1). Common themes relate to tracking the source of APIs and strengthening the requirement or incentive to purchase U.S.-made medications. Although such actions have the potential to improve the safety and security of the USPSC, policy alone is unlikely to fix our fractured supply chain. Mandating that any organization that purchases medication "Buy American" in the absence of

Table 1
Proposed Congressional legislation related to the pharmaceutical supply chain

Legislation	Introduced by	The bill would:
Protecting our Pharmaceutical Supply Chain from China Act[45]	• Tom Cotton (R-AR) • Marsha Blackburn, (R-TN)/Ted Cruz (R-TX)	Track active pharmaceutical ingredients through an FDA registry. Prohibit pharmaceutical purchases from China or products with active pharmaceutical ingredients created in China. Create transparency in the supply chain by instituting a country-of-origin label for all imported drugs. Provide economic incentives for manufacturing drugs and medical equipment in the United States.
Strengthening America's Supply Chain and National Security Act[46]	• Marco Rubio (R-FL)	Direct the DoD to determine the extent of its dependency on foreign sources of drugs. Require pharmaceutical companies to provide FDA with information to determine volume of APIs used in pharmaceuticals. Restore Buy American Act's intent for DoD and VA.
Securing America's Pharmaceutical Supply Chain Act[47]	• John Garamendi (D-CA) • Pete Stauber (R-MN)	Require federal agencies to preferentially purchase medications made in the United States when available.
Securing America's Critical Minerals Supply Chain Act[48]	• Pete Stauber (R-MN)	Provide a tax deduction for domestically produced pharmaceutical raw materials.
Pharmaceutical Independence Long-Term Readiness Reform Act[49]	• John Garamendi (D-CA)	Require the DoD to purchase U.S.-made raw materials, medicines, and vaccines, and identify vulnerabilities related to dependence on Chinese pharmaceuticals.

Abbreviations used: R-AR, Republican-Arkansas; R-TN, Republican-Tennessee; R-FL, Republican-Florida; R-TX, Republican-Texas; D-CA, Democrat-California; R-MN, Republican-Minnesota; DoD, Department of Defense; FDA, Food and Drug Administration; API, active pharmaceutical ingredient; VA, Department of Veterans Affairs.

increased domestic manufacturing capacity has the potential consequence of precipitating or exacerbating shortages. Economic incentives coupled with domestic manufacturing would be a preferred strategy for success.[33] Advanced manufacturing technology such as pharmacy on demand also has the potential to revolutionize the manufacturing process, shifting away from traditional batch manufacturing methods to continuous-flow synthesis.[34] The technology has demonstrated the ability to reduce the time required to manufacture several different medications in a short period of time but will likely require additional research and investment.

Pharmacists and pharmacy technicians are on the front line

In parallel with innovative policy, scientific, and economic support, there are several activities that pharmacists can perform to safeguard the USPSC. Pharmacists already add value by identifying therapeutic alternatives in cases where medications are not available owing to shortage or recall.[13] Patients continue to trust their pharmacists who are often the first to hear of and report problems with medications.[35] The Pharmacists' Patient Care Process can be a helpful framework to address medication-related quality or safety issues, and pharmacists should continue to report these issues to MedWatch or other appropriate data repositories.[36,37]

Pharmacists involved with purchasing medications can screen manufacturers and ask what "backup capability" they have to produce medications. A company with backup capability will be able to provide an uninterrupted supply of medication even if, for example, a production facility experiences a problem (e.g., natural disaster, public health crisis). Pharmacists can review information on drug recalls on FDA's Recalls, Market Withdrawals, & Safety Alerts website, and information on drug shortages on the American Society of Health-System Pharmacists website.[38,39] Pharmacists can also review FDA warning letters and inspection records before buying from a particular manufacturer. A simple search in the documents for key words such as "sterility" or "data integrity" can identify red flags.[40,41] One example of this information being put into action involves pharmacists partnering with physicians to use market intelligence to inform purchasing on the basis of corporate reputation and safety signals.[8]

There may be instances where pharmacists want to play a role in purchasing medications but are unable to do so because of the corporate structure of their organization. In these situations, the pharmacist may have to get creative and leverage informal leadership skills to enact change. If a pharmacist has a patient safety concern or is receiving several reports from patients experiencing problems with a particular manufacturer or medication, it is still important to report these events through MedWatch or their local patient safety reporting system. Several recent recalls for medications such as valsartan, ranitidine, and metformin were brought to FDA's attention through a citizen's petition.[42]

Pharmacists should continue to engage in conversations on the appropriateness of a drug substitution, particularly in the case of narrow therapeutic drugs or high-risk situations such as post-organ transplantation. If a substitution is made, pharmacists should follow up to assess if the patient is better, worse, or the same. This applies both when switching from brand to generic or generic to generic. Transitions of care can be a particularly vulnerable time for a patient.[43] One question a pharmacist might ask is, "Will the patient receive the same medication (i.e., brand or generic) in an inpatient versus outpatient setting?" Although pharmacists often have little choice in the matter, they can certainly be aware of the issue and use their clinical judgment to determine the best course of action. An example of this is highlighted by the role that pharmacists can play in ensuring that their patients with

seizures continue to receive the same drug formulation by the same manufacturer month-to-month. Pharmacists can also educate and advise patients and prescribers on how to deal with a recall. In the case of ranitidine and valsartan, a pharmacist can recommend a therapeutic alternative in the same class. In the case of metformin, pharmacists[32] could help determine if the patient received a recalled lot and assist with transitioning them to a product made by a manufacturer that was not affected by the recall.

Given the increased media attention around this issue, pharmacy professionals might anticipate that the public may start seeking answers regarding the source or availability of their medication. Pharmacists can attempt to ask the manufacturer, distributor, or packager where the FDP and API are made, although, as discussed previously, some companies may not have, or be willing to disclose, this information. If this is the case, the National Institutes of Health's DailyMed website may be an additional resource for this information, given that it maintains accurate drug labels that can be a source of manufacturer or distributor information.[44]

Conclusion

The USPSC is complex, global, and goes beyond FDPs. Protecting it will require innovative solutions, including legislation, policy, market incentives, and objective surveillance testing. The 2020 APhA HOD has asserted that "The quality and safety of pharmaceutical and other medical products and the global pharmaceutical and medical product supply chain are essential to the United States national security and public health." Pharmacy professionals on the front line improve the health of patients, identify medication-related issues, and engage in drug-procurement decisions. Pharmacists are uniquely qualified to lead our nation's effort to safeguard the USPSC through advocacy, education, and engagement.

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Ryan C. Costantino, MS, PharmD, BCPS, BCGP, Branch Chief, Data Innovation, Enterprise Intelligence and Data Solutions, Defense Health Management Systems, San Antonio, TX