

## Global Medical Supply Chain Security

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## AMA Journal of Ethics®

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### FROM THE EDITOR

## Why Should Clinicians Care About Global Medical Supply Chain Security?

Amy B. Cadwallader, PhD

### Framing the Conversation

A common adjective used to describe the global medical supply chain is “complex,”<sup>1</sup> due to its length and interdependence not only among supply chain segments, but among nation states. Myriad international experts exchange ideas about vulnerabilities of medical supply chains and how to make them more resilient. But why should clinicians care about a topic seemingly so far removed from patient care? And why is this an ethical issue?

One reason is that all clinicians should be aware of weaknesses in medical product supply chains because breaks in those chains generate **drug shortages**; increase prevalence of **substandard**, falsified, or counterfeit medicines; and compromise availability of devices and personal protective equipment. When medical supply chains break, clinicians’ ethical decisions are made more fraught by threats to their abilities to meet care standards as they manage patients’ care and try to respond to patients’ needs. This issue of the *AMA Journal of Ethics* explores this and kindred problems and questions.

### Global Medical Supply Chain Complexity

Understanding risks to and resiliency of drug supply chains is inherently interdisciplinary and requires diverse perspectives, multiple stakeholders’ input, and global coordination. A sufficiently integrated approach to medical supply chains’ management requires understanding how those chains are enmeshed in a global context. For example, the SARS-CoV-2 pandemic highlighted medical supply chains’ interconnectedness and complexity, which was heightened by nation states’ interdependence and, often, fraught geopolitical relationships.<sup>2,3</sup> The interconnectedness of global medical supply chains became remarkably apparent during the pandemic when many frontline health care professionals did not have personal protective equipment, such as surgical masks and gowns, because of shortages driven by pandemic-related supply disruptions and increases in demand. Supply shortages and increased global demand also caused surges in these items’ prices when, if ever, they became available.<sup>3</sup>

This complexity leads to—as clinicians who worked during the pandemic know well—drug shortages that, although increasingly more noticeable due to media attention, have been pervasive problems for many years.<sup>4,5,6</sup> For example, older sterile injectable

medicines have been in short supply frequently over the past several years despite their need and use as first-line, essential medicines to provide support care for and treat many conditions, including pediatric oncology.<sup>5</sup> Clinicians and their patients should be able to trust that they will have access to basic, quality medicines, but this is no longer reliably the case, even in wealthy areas of the world.

Additional questions include these: *Why do supply chain disruptions happen? Who should be responsible for their smooth operation when so many patients and clinicians rely on them? How should known present risks be mitigated? How should supply chain participants be positioned to better anticipate and respond to **unknown future risks**?* Good responses to these questions must address supply chains' vulnerabilities. Given the complexities just named, assigning responsibility to any single entity would likely be as shortsighted and oversimplified as a failure to draw on the plurality of perspectives needed to generate possible solutions.

### **Need to Build Resilience**

Many groups are evaluating how to bolster medicines supply chains in their respective countries, regions, or industries.<sup>1,7,8,9,10,11,12,13</sup> Dozens of reports and publications have been released in recent years that focus on supply chains for medical products, including drugs, biologics, personal protective equipment, devices, and other equipment.<sup>1,7,8,9,10,11</sup> (See also **Supplementary Appendix**.) Some reports were written in the early days of the SARS-CoV-2 pandemic and focused on ramifications of significant, rare events, including supply disruptions, especially those stemming from importation policies and practices.<sup>14,15,16</sup> Other publications, many written during later stages of and recovery from the pandemic, reported on unexpected spikes in demand for medicines and medical products and commented on preparedness, essential medicines, and renewed consideration of emergency stockpiling.<sup>10,16,17,18,19,20,21,22</sup> More recent reports have evaluated long-standing vulnerabilities in medical supply chains that were worsened by events of the past several years.<sup>7,23,24</sup> These reports—authored by government agencies, academicians, think tanks, consulting companies, and other supply chain stakeholders—identify supply chain vulnerabilities and offer recommendations to improve domestic and global medical product supply chain resilience. Importantly, improvements suggested in these reports tend to reflect their sponsors' or authors' vantage points, which focus narrowly on what *they* can do to advance supply chain resilience. These many initiatives emphasize the need for progress, while underscoring the pressing need for better coordination and more effective forging of solutions that fit together and meaningfully address key gaps in medical supply chains.

### **When Supply Chains Vulnerabilities Compromise Clinical Practice**

This theme issue considers clinical and ethical demands faced by clinicians trying to care well for patients, manage drug shortages in a hospital, ration limited supplies of key medicines and equipment, and manage consequences of quality control failures or compromised stockpile access. Contributors to this issue attempt to reframe essential medicines conversations and ask, *Why don't essential medicines lists take supply chain security risks into account?* Health care policy and supply chain experts discuss **implications of importing medicines**, how currently siloed data can be more effectively and efficiently shared to promote understanding of risks to medical supply chains' integrity, and obstacles to supply chains' security, even in the final miles of getting medicines to patients.

Clinicians can reasonably be expected to be experts in caring for patients, not in managing global medical supply chain security. However, since clinicians and their patients feel the effects of compromised supply chains, this issue is intended to be a resource for clinicians looking to better understand how supply chains inform their capacity to care well for patients. Hopefully, this issue will support clinicians' appreciation of a bigger picture behind challenges they will continue to face until health care system infrastructures bolster the security, resilience, and reliability of global medical supply chains.

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**CASE AND COMMENTARY: PEER-REVIEWED ARTICLE**

**Which Drugs Should Be on the Essential Medicines List?**

Courtney Perlino, MPP, Hilary Daniel, and Amy B. Cadwallader, PhD

**Abstract**

The World Health Organization (WHO) published its first Essential Medicines List (EML) in 1977, and it is updated biennially. One might reasonably think drugs on the EML are there because they are critical to effective, evidence-based patient care and intervention. One might not reasonably guess, however, that a particular drug's supply chain vulnerabilities that make it a shortage risk would contribute to a drug's listing on the EML. This commentary on a case first describes why the WHO makes the EML and suggests reasons why it might be important to consider a drug's shortage risk when revising and updating it. This commentary also suggests how distinguishing "essential" drugs from "vulnerable" drugs could bolster supply chain resiliency and mitigate drug shortages' disruptions to patient care.

**Case**

Dr C is an oncologist at an academic health center who has practiced for 15 years. Dr C's patient is JJ, a child newly diagnosed with cancer. Dr C has now received a second notice from the hospital pharmacy that a standard chemotherapeutic intervention drug, cisplatin, for the treatment of JJ's cancer is in short supply. Dr C starts planning ahead and wonders whether and how to adapt JJ's—and possibly her other patients'—care plan, perhaps by omitting at least one of JJ's chemotherapy cycles or by limiting other patients' access to the drug by modifying their treatment plan so that JJ's care plan is not altered.<sup>1,2</sup>

**Commentary**

Suppose Dr C has faced this issue several times before, as shortages of several oncology medications have persisted for decades,<sup>3</sup> and remembers the impacts on patients—and the impacts on *her* of not being able to provide the best care for her patients—of the shortages of various oncology drugs. She therefore decided to look into the reasons why medicines critical to her patients' treatment regimens are often unavailable. The exact reasons were difficult to find, but she learned that a major reason for shortages in the past was supply chain issues, including problems with manufacturing processes, increased demand, and shortages of the necessary active pharmaceutical ingredients. In the end, though, all that she knows is that the supply chains for numerous cancer drugs need strengthening. They should not be bending or breaking this frequently, to the detriment of her patients, who are among the sickest in

her hospital and for whom timely treatment with the most effective therapies is absolutely essential.

Dr C's analysis of data revealed that pediatric oncology drugs have a 90% higher likelihood of a shortage event than the average drug and have few or no therapeutic alternatives.<sup>4</sup> These treatment shortages lead to delays in chemotherapy, changes in treatment regimens, missed treatments, complicated clinical research, increased risk of medication errors, adverse outcomes, and even patient death.<sup>5</sup> Dr C has also read news articles about the federal government and Congress taking action on drug shortages. A lot of what she has read has been about ensuring the availability of drugs deemed essential in times of crisis and medical countermeasures to ensure reliable and resilient supply chains. The focus of efforts to date seems to be on identifying and preventing shortages of critical medicines during public health emergencies, natural disasters, or geopolitical threats, rather than on what she and her patients experience every day. One article linked to essential and critical products lists recently developed by federal agencies, but Dr C found that many of the drugs used in the treatment of her patients were not included on the lists. She struggles with this focus and approach, as it sends a message that the cancer drugs that she relies on to treat her patients, many of whom are children, are not essential or as high of a priority as other drugs or have supply chains that are not worth investing in and strengthening. Dr C understands the need for the nation to be able to have critical medicines during public health emergencies but believes her patients should not be left behind in these efforts to prevent or mitigate drug shortages and ensure medicine supply chain resiliency.

While current research is evaluating strategies to [manage these drug shortages](#),<sup>6</sup> better, more enduring solutions are required to ensure that all patients have access to the medicines they need. In what follows, we examine differing policies and explore better ways to balance public health needs in times of uncertainty or crisis and to ensure an appropriate supply of critical medicines, as well as medicines with vulnerable supply chains, that are crucial to the everyday lives and well-being of patients.

### **What's "Essential"?**

The World Health Organization (WHO) published its first Essential Medicines List (EML) in 1977, and the first Essential Medicines List for Children was published in 2007.<sup>7</sup> These lists are updated every 2 years and "aim to address global health priorities, identifying the medicines that provide the greatest benefits, and which should be available and affordable for all"<sup>8</sup> and are "intended to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford."<sup>9</sup> WHO EMLs guide the development of country-level EMLs, which influence national formularies, prescribing and practice guidelines, and price negotiation and procurement mechanisms,<sup>8</sup> although considerable variation exists in the medicines included on country-level EMLs.<sup>10</sup> The creation of EMLs was historically considered a public policy intervention to prevent and mitigate drug shortages by identifying those drugs that are vital to addressing the health care needs of populations and by guiding governments' and purchasers' prioritization of medicines and interventions necessary to support public health and encourage favorable health outcomes.

How "essential medicines" are defined, what drugs are included on EMLs, and the stated purpose of EMLs are critical questions, as they are directly linked to and serve as the impetus for numerous policy efforts and initiatives to improve medicine supply chain

resiliency, including investments in innovation, stockpiling considerations, and trade decisions, which may ultimately affect the availability or accessibility of these medicines to clinicians and patients.<sup>11,12,13,14,15,16,17</sup> While the WHO EMLs were referenced as a starting point for such lists, country-level EMLs have evolved to include critical drugs needed for emergency response and for saving and preserving life.<sup>11,18</sup> The onset of the SARS-CoV-2 public health emergency and its impact on pharmaceutical supply chains brought the concept of essential medicines into sharp focus.

### **Policies Related to Essential Medicines**

Two recent supply chain executive orders issued in the United States each had different aims, which affected the focus and content of critical product lists that the US Food and Drug Administration (FDA) and the US Department of Commerce (Commerce) put forward. The first, Executive Order on Ensuring Essential Medicines, Medical Countermeasures, and Critical Inputs Are Made in the United States (EO 13944), “directed the ... FDA to identify a list of essential medicines, medical countermeasures and critical inputs that are medically necessary to have available at all times in an amount adequate to serve patient needs and in the appropriate dosage forms.”<sup>19</sup> The stated goal of the list was “to ensure the American public is protected against outbreaks of emerging infectious diseases, such as COVID-19, as well as chemical, biological, radiological, and nuclear threats.”<sup>19</sup> Previously, the FDA did not maintain this type of EML. As a result of EO 13944, the FDA published a list of 227 drug and biological product essential medicines and medical countermeasures, as well as 96 device medical countermeasures.<sup>20</sup> The second, Executive Order on America’s Supply Chains (EO 14017), focused and expanded on the potential and real impacts of pandemics and other biological threats, cyberattacks, climate shocks and extreme weather events, terrorist attacks, geopolitical and economic competition, and other conditions bearing on manufacturing capacity and supply chain resiliency in multiple industry sectors.<sup>21</sup>

Subsequent to EO 14017, the US Department of Health and Human Services (HHS) directed a review of the FDA EML and recommended that 50 to 100 most critical drugs from the FDA list be available at all times for US patients because of their clinical necessity and lack of therapeutic redundancy (Critical Drug List). The resulting list was narrowed down to 86 critical medicines for acute patient care.<sup>12</sup> Also fulfilling the intent of EO 14017, Commerce developed a list of critical goods, including medicines, intended to “serve as a tool to facilitate ongoing targeted analysis of trade data and the evaluation of policies to strengthen these supply chains.”<sup>22</sup> Because of the different objective of the Commerce list, the drugs on this list differ from those included on the FDA list or the HHS Critical Drug List. For example, only one chemotherapeutic drug, cyclophosphamide, is included on both the FDA list and the Critical Drug List, but it does not appear on the Commerce list.

Therefore, what are considered essential medicines—and the purposes of EMLs—if not properly defined, can leave countries, regions, or the world unprepared or underprepared or cause initiatives and finite resources to be potentially misdirected. For example, if EMLs only focus on medicines critical to responding to public health **emergencies or national disasters**, then countries may not be adequately prepared to prevent or mitigate drug shortages of more commonly used drugs that are life-supporting, life-sustaining, or intended for use in the treatment of a debilitating disease or condition, including pediatric oncology drugs. Medicines with the most vulnerable supply chains that have the highest likelihood of breaking in the event of an unexpected shock—vulnerable medicines—should be considered an integral part of the exercise to

establish EMLs. If the evaluation of essential medicines is based not only on clinical importance and demand indicators, but also on their supply chain vulnerabilities, then domestic, regional, and global supply chain resiliency efforts can be better informed, designed, and implemented—resulting in better outcomes for patients.

### **Incorporating Supply Chain Risk**

There is no common definition of or approach to EMLs within the United States, across countries and regions, and globally. However, there is a common shortcoming of EMLs generally: a medicine's risk of shortage, or supply chain vulnerability, is not adequately factored into whether a medicine is included on the list. A disconnect between medicines identified as being "essential" and medicines in short supply has been reported: of the 276 drugs that were in short supply in 2021 in the United States,<sup>20,23,24</sup> only 86 were on the FDA Essential Medicines, Medical Countermeasures, and Critical Inputs List.<sup>20</sup>

Medicines with vulnerable supply chains can also be among those already included on an EML, but there must be a broader recognition that medicines with vulnerable supply chains can cause patient harm and should be factored into how products are considered for inclusion on essential or critical medicines lists. Both demand-side analysis and supply-side analysis are needed to prioritize medicines and target policy interventions to prevent and mitigate drug shortages and improve medicine supply chain resiliency, including for essential medicines and vulnerable medicines. Factoring vulnerable medicines into the conversation can potentially help bolster the visibility and supply of those medicines, which have been notoriously present on drug shortage lists and are needed to support patient care—and without which public health crises may emerge.

### **Conclusion**

When drugs are in short supply, clinicians must often make **difficult decisions** about how to treat their patients, given limited or inconsistently available options, and these decisions can potentially result in suboptimal outcomes. Clinicians are not expected to understand the nuances of the supply chains that provide the resources they require to treat their patients, but it can be useful to understand EMLs, how they are developed, and their implications for the availability and accessibility of medicines. Considering both essential medicines and vulnerable medicines will enable a more comprehensive strategy for preparedness initiatives, minimizing drug shortages, and bolstering supply chain resiliency—and will ultimately ensure that more patients' medicine needs are met.

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**CASE AND COMMENTARY: PEER-REVIEWED ARTICLE**

**How Should Regulators and Manufacturers Prevent Avoidable Deaths of Children From Contaminated Cough Syrup?**

Kavitha Nallathambi, MPH, MBA and Amy B. Cadwallader, PhD

**Abstract**

This commentary responds to a case about diethylene glycol-contaminated glycerin in cough syrup. Glycerin is a commonly used excipient in medicines to improve texture and taste. Excipients are typically pharmacologically inactive ingredients contained in prescription and over-the-counter drugs that play a critical role in the delivery, effectiveness, and stability of active drug substances. The commentary first canvasses how contaminants enter the excipient supply chains. One way is by misleading labeling or intentional adulteration by manufacturers or suppliers. Another way is by human or systemic error. This commentary then discusses quality control testing and suggests the ethical and clinical importance of increased transparency in excipient supply chains.

**Case**

Shortly after returning home to the United States from a vacation in Bali, Indonesia, with her 2-year-old daughter, JJ, K brought JJ to an emergency department (ED) because JJ was dizzy, complained of headache, and vomited at the airport. JJ had developed a mild cough and congestion while in Indonesia, so K bought cough syrup for JJ at a pharmacy in Indonesia and administered it to JJ before boarding their return flight to the United States. US State Department travel advisories caution that local pharmacies in Indonesia carry “a range of products of variable quality, availability, and cost,” and “counterfeit pharmaceuticals are a significant risk.”<sup>1</sup>

Dr ED documented JJ’s symptoms of tachycardia, acidotic breathing, pallor, edema, and hepatomegaly as acute signs of toxicity, including liver failure.<sup>2</sup> ED staff suspected JJ had diethylene glycol (DEG) poisoning. K gave the cough medicine bottle to ED staff and felt devastated when she learned of the possible long-term complications JJ could suffer from DEG poisoning.

**Commentary**

Glycerin is a common excipient used to aid in thickening liquid medicines and to provide a soothing film for some medicines, including cough medicines and artificial tears.<sup>3</sup> Glycerin is produced from the hydrolysis of fats and oils, and a majority of the glycerin

used in medicines is a byproduct of the biodiesel and oleochemical manufacturing industries.<sup>4</sup>

DEG is the most common contaminant found in glycerin. It has thickening and soothing properties, similar to glycerin. DEG is an industrial solvent used in “antifreeze and as a raw material for manufacturing polyester fibers.”<sup>5</sup> Companies sometimes use DEG as an illegal adulterant in liquid medicines, such as cough syrups, because it is a cheaper alternative to nontoxic solvents such as glycerin. DEG ingestion can lead to acute renal failure, which can cause permanent disability or death.<sup>5</sup>

DEG can find its way into the supply chain in several ways—through intentionally or accidentally mislabeled products, through accidental contamination due to human error, or through intentional adulteration by manufacturers or suppliers to achieve higher profits. Economically motivated adulteration can be driven by opportunity or lack of transparency and traceability in the supply chain.

DEG contamination cases highlight the challenges of assuring medicines’ quality in a complex global supply chain. This commentary will discuss considerations in and implications of quality control testing, public quality standards, and increased transparency in the global supply chains of medicine ingredients.

### **DEG Deaths**

In 2022, a number of countries reported incidents of over-the-counter cough syrups for children being contaminated with toxic levels of DEG and ethylene glycol (EG), resulting in over 300 child deaths in The Gambia, Indonesia, and Uzbekistan.<sup>6</sup> The World Health Organization (WHO) issued 5 medical product alerts towards the end of 2022 and through mid-2023 to address these incidents in the affected countries.<sup>6,7</sup> Health officials in Indonesia temporarily stopped the sale of some syrup-based medications following the deaths of 144 children.<sup>8</sup> Laboratory analysis in The Gambia found that product samples contained unacceptable amounts of DEG.<sup>9</sup> These cough syrups were discovered to be imported from India.<sup>10</sup> In addition to the recent tragedies, past DEG-related incidents have also been reported in Panama, China, Haiti, Bangladesh, Argentina, Nigeria, and India. For example, in 2006, at least 78 children died from DEG poisoning in Panama as a result of contaminated cough syrup traced to a factory in China that mislabeled DEG as glycerin.<sup>11</sup> Some of these countries have a history of multiple events even though these incidents are preventable using the right quality controls and risk assessments.

### **How Contaminated Products End Up on the Market**

The onus is on drug manufacturers to perform identity testing on glycerin raw material—including tests to quantify the amount of DEG present and to verify the purity of glycerin to be used in pharmaceutical products. Typically, shipments of glycerin for use in pharmaceutical manufacturing are accompanied by a certificate of analysis (COA) from the supplier. COAs certify that the product was tested and found to comply with the specifications set forth by national regulatory authorities (NRAs), such as the US Food and Drug Administration (FDA).

Quality issues related to impurities and intentional adulterants can be found in products used by consumers due to a number of factors, ranging from manufacturing and supplier issues to gaps in regulatory capabilities. As products pass through the supply chain, COAs can be produced and reproduced without independent testing. In addition,

there can be opacity about the actual substance produced, the naming and labeling process, licensing or registration of the facility, and responsibility for ingredients upstream in the supply chain. Robust quality assurance programs and supplier qualification programs are often lacking. The situation is further hampered by a lack of traceability in the supply chain. Discrepancies, such as those noted for COAs, in the supply chain can have an impact on product quality.

### **What Can Be Done?**

Industry and regulators should take a risk-based approach and stop preventable deaths by expanding quality testing to the upstream supply chain. Such testing is required for certain products marketed in the United States. However, not all countries—and, in particular, not all low- to middle-income countries (LMICs)—have the same quality assurance requirements and resources. Controlling the quality of raw materials is essential for maintaining safety and ensuring consistency across batches. Although quality testing across the product life cycle is heavily focused on the active ingredient and the final product, failures of products can be caused by excipients and by nonactive and raw materials as well.

*What should government regulators do?* The NRAs in the health systems of governments have a critical role to play in protecting patients from harm. Governments should implement regulations with provisions for upstream, risk-based quality testing of raw materials; strengthen national regulatory systems, including having in place quality control laboratories; invest in risk-based postmarketing **surveillance** to test products after they are on the consumer market and available for sale; and impose stronger penalties for failures in quality to prevent avoidable deaths, particularly in countries that appear to be at risk for repeated incidents.

*What should manufacturers and suppliers do?* Patient safety begins in the supply chain with manufacturers and suppliers. Impurities and other **adulterants in raw materials** pose potential health threats when present in the manufacturing of active pharmaceutical ingredients (APIs) and finished drug products. Manufacturers can verify the suppliers and have an audit system in place; implement a raw material qualification program; test the incoming raw materials; invest in tools for quality assurance; and understand their manufacturing processes to eliminate impurities. For example, testing of key starting materials, APIs, excipients, and inactive ingredients by the manufacturer to verify the information on COAs should be used to detect the presence of DEG and other contaminants and impurities. In these ways, manufacturers can protect their supply chains adequately from risk of adulteration.

*What should patients do?* Patients should be aware of the risks associated with some medicines that are purchased from nonreputable retail locations, online, or when travelling or that are imported. Even if staff members at the hotel K was staying at had assured her that the pharmacy they recommended was a reputable place to purchase medicines and the pharmacist in the store had not realized substandard medicines were being sold, K purchased contaminated medicine and gave it to JJ. Patients should be aware that drug standards and regulations vary from country to country and that drugs sold outside the United States or from some online sources may not meet FDA standards for safety and effectiveness. The FDA generally does not evaluate medications manufactured solely for marketing and use in other countries for safety and effectiveness.<sup>12</sup> Patronizing only reputable pharmacies is therefore prudent for patients.

*Resources needed for strong quality controls to protect patients.* Public quality standards, such as those developed by US Pharmacopeia (USP), are a statutory requirement created in the federal Food, Drug, and Cosmetic Act of 1938 and used globally to help ensure the identity, purity, strength, and quality of medicines and the safety of patients. These quality standards apply across the entire medicines supply chain from raw materials to distribution. Standardization of raw materials (components) allows for the control of consistency in manufacturing of finished products. Building and funding regulatory capabilities, including pharmacopeial standards that can serve as tools for compliance with regulatory requirements, is essential. Support can focus on improving quality assurance systems, such as through regulatory systems strengthening, the provision of technical assistance to develop capabilities of national drug labs, training for national lab scientists, and WHO prequalification for essential medicines and postmarket surveillance. For example, following the WHO's urgent call to action regarding DEG and EG contamination in January 2023,<sup>6</sup> USP, an independent, scientific, nonprofit that sets standards for medicinal quality, developed a free tool kit to support manufacturers, regulators, and global pharmacopeias in addressing DEG contamination associated with allergy, cold, and cough medicines.<sup>13</sup>

### Call to Action

All patients, all over the world, have a human right to safe and effective medicines they can trust. There is an ethical imperative to ensure **access to quality-assured medicines** and ingredients. This case highlights another reminder to appropriately fund, provide resources to, and build capacities of regulators in every country, including LMICs, to best position them to detect, prevent, and respond to dangerous products, such as those containing DEG. Given the complex pharmaceutical supply chain, there is a clear need for greater regulatory focus on strong quality controls for raw material and finished product testing. In addition, pharmaceutical manufacturers and suppliers must live up to their responsibility when it comes to producing safe, quality products. Closing quality gaps for pharmaceutical ingredients will better protect patients and help prevent tragedies like the childhood deaths in The Gambia, Indonesia, and Uzbekistan.

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**HEALTH LAW: PEER-REVIEWED ARTICLE**

**What Should Prescribers and Policy Makers Know About US Drug Importation?**

Nisha Quasba, MPH and Elliot Vice

**Abstract**

Drug importation raises several ethical and safety concerns relevant to prescribers and policy makers considering costs and benefits of international medicine importation. This article suggests key points to consider, especially from a policy perspective, when weighing imported medicines' perceived affordability and accessibility against additional resource expenditure needed to assure sufficient regulatory oversight and equitable distribution and to mitigate potential risks of harm to patients.

**Federal Drug Importation Regulation**

The rising cost of prescription drugs poses affordability challenges for both patients and the federal government, with the United States spending more on prescription drugs per capita than other high-income countries.<sup>1</sup> As prices of certain drugs outpace inflation,<sup>2</sup> the federal government has attempted to curb this trend by using drug importation as a potential policy lever. Since 2003, the US Food and Drug Administration (FDA) has had the legal authority to allow wholesale importation of prescription drugs from Canada, thanks to the Medicare Prescription Drug, Improvement, and Modernization Act passed by Congress.<sup>3</sup> In 2020, the FDA and the Secretary of the US Department of Health and Human Services (HHS) issued a rule to implement this provision, thereby permitting the importation of specific prescription drugs from Canada under Section 804 of the Food, Drug, and Cosmetic Act, known as the Section 804 Importation Program (SIP).<sup>4,5</sup> The aim of the SIP was to “achieve a significant reduction in the cost of covered products to the American consumer with no additional risk to the public’s health and safety.”<sup>6</sup> However, drug importation raises several ethical and safety concerns, necessitating that perceived affordability and accessibility of imported medications be weighed against their potential risks to patient safety, lighter regulatory oversight, and potential for inequitable distribution.

**SIPs**

Implementing a SIP requires SIP sponsors (states) not only to create their own importation program but also to submit it to the FDA for approval prior to proceeding with implementation. A state’s proposal must list specific, eligible prescription drugs for the SIP; identify a Canadian foreign seller to procure directly from manufacturers; and

designate a US importer that will buy the drug directly from the foreign seller.<sup>4</sup> Since the rule establishing the SIP went into effect, several states—including Vermont, Colorado, Florida, Maine, New Hampshire, New Mexico, North Dakota, Texas, and Wisconsin—have passed laws allowing them to submit SIP proposals to the FDA for approval, and 6 of them have submitted proposals and are awaiting FDA approval.<sup>7,8</sup> Designing a state-operated program that can guarantee adherence to FDA standards regarding authenticity, purity, potency, and lack of adulteration<sup>9</sup> while still achieving cost savings for consumers is a challenge.

Since the rule took effect, only Florida's SIP proposal has been approved by the FDA,<sup>10</sup> casting doubt on the likelihood of such approval in the future. Despite its intent to reduce drug costs without compromising public safety, the rule has aroused concerns about potential risks to public health that have been repeatedly emphasized by the FDA and public health leaders from both political parties.<sup>11</sup> Supporters of drug importation argue that circumstances have changed since the authority was granted,<sup>6</sup> but, unfortunately, risk of counterfeit products entering the supply chain remains.

### Counterfeit Drug Risks

The process proposed by the FDA in the 2020 final rule requires the cooperation of Canadian suppliers for drug importation. However, considering that Canada has a population of only 38.9 million,<sup>12</sup> one-tenth that of the United States, the National Association of Pharmacy Regulatory Authorities in Canada deems it improbable for the Canadian pharmaceutical market to absorb the substantial drug demand from the United States.<sup>13</sup> One study estimated that US importation of 46 Canadian drugs would exhaust supplies for most of them in less than 3 months.<sup>14</sup> Importantly, the combined population of 5 states—Florida,<sup>15</sup> Vermont,<sup>16</sup> Maine,<sup>17</sup> New Mexico,<sup>18</sup> and Colorado<sup>19</sup>—that have passed importation legislation exceeds 30 million people, which is more than 80% of Canada's total population. The Canadian government vehemently opposes US federal and state action that encroaches on its drug supply, contending that such policy could exacerbate Canada's chronic **drug shortage problem** and jeopardize the health of Canadians.<sup>20</sup> In fiscal year 2019 to 2020, shortages affected nearly a third of all the prescription medicines sold in Canada,<sup>21</sup> with 2700 drug shortages in fiscal year 2022 to 2023.<sup>22</sup> These shortages hit consumers, as a 2018 national survey published by the Canadian Pharmacists Association revealed that 1 in 4 Canadians had either personally experienced or knew someone who had faced a drug shortage in the past 3 years.<sup>23</sup> Canada's drug shortages raise concerns about equity and fairness in the global distribution of pharmaceuticals, as importing countries like the United States could inadvertently reduce the availability of drugs in countries where they are manufactured or originally intended for sale.

In addition to exacerbating drug shortages in Canada, allowing drug importation from Canada could potentially open the way for counterfeit drugs to enter the US market. Canada has acknowledged its inability to monitor the safety of medicines destined for the United States,<sup>24</sup> placing the responsibility on American authorities to ensure the safety of imported drugs. US law enforcement<sup>25,26</sup> has already come out in opposition to drug importation, highlighting that the influx of drugs from other countries would only shift costs and burden to law enforcement while simultaneously increasing the risk of illegitimate products entering the country. While some might believe that limiting imports to drugs manufactured in Canada enhances safety for US consumers, in reality, drugs labeled as *from* Canada could originate from any country and pass through Canada during shipment to the states. Canadian law permits the "transshipment" of

drugs from many countries, including from those with lower regulatory standards.<sup>27</sup> These countries might not have a Mutual Recognition Agreement with Canada to ensure reliance on its regulatory system for prescription medicines. Importing drugs from foreign countries thus effectively bypasses the regulatory oversight and approval processes and raises concerns about the government's ability to ensure the safety, efficacy, and proper labeling of imported drugs.

### **Leading Patients to the Internet**

Approval of the drug importation rule has erroneously led consumers to believe they can obtain their medications from online pharmacies, despite the rule explicitly prohibiting it.<sup>28</sup> Significantly, 96% of online pharmacies on the National Association of Boards of Pharmacy® Not Recommended List do not require a valid prescription.<sup>29</sup> Moreover, the IQVIA Institute for Human Data Science estimated that 12.6% of adverse events from 2017 to 2022 could have been avoided had all drugs purchased from illegal online pharmacies instead been purchased legally.<sup>30</sup> These adverse events contributed an additional \$67 billion in costs to the US health system and resulted in an estimated loss of \$34 billion for legitimate pharmaceutical businesses in 2022.<sup>30</sup> While the US government can and does take action against illegal online pharmacy operators within its borders, its jurisdiction ends there. Although there have been instances in which foreign jurisdictions collaborated with the United States on enforcement actions, many international criminal internet drug sellers continue to evade capture.<sup>29,31,32</sup>

An illustrative example of collaborative enforcement is a 2015 case involving Canadadrugs.com. In this particular case, the US Department of Justice brought charges against companies and individuals affiliated with Canadadrugs.com for smuggling \$78 million worth of mislabeled, unapproved, and counterfeit cancer drugs into the United States.<sup>33,34</sup> To expand its operations to physicians' offices in 2009, the company reportedly utilized subsidiaries based in Barbados and the United Kingdom (UK).<sup>35</sup> These subsidiaries, along with the parent company, allegedly shipped illegally imported medicines through the UK to drop shippers situated at 3 US locations. Of the 14 defendants, only 1 was based in the United States.<sup>34</sup> To apprehend the remaining 13 defendants located in different countries, law enforcement sought the cooperation of foreign nations through extradition treaties. The company's website closed in 2018,<sup>36</sup> and the founder of the company received a relatively lenient sentence,<sup>33</sup> which many perceive as an insignificant consequence for the company's actions.

### **Cost Savings?**

While drug importation can be perceived as a means to address high drug prices and access, it might not necessarily lead to sustainable, long-term solutions and could potentially undermine policy efforts to address pricing and access issues by diverting attention from systemic reforms within the health care system. The rule establishing SIP explicitly states that the potential cost savings from drug importation could not be estimated,<sup>4</sup> and previously the Congressional Budget Office had concluded that importation policy would "produce at most a modest [cost] reduction."<sup>37</sup> The idea of accessing cheaper drugs from Canada might seem straightforward, but the actual importation process incurs additional costs such as packaging, testing, shipping, and compensation for intermediaries, which ultimately add to the price.

Costs and cost savings are also relative. In a 2017 interview, George Karavetsos, the former head of the FDA's Office of Criminal Investigation, emphasized that implementation costs of state importation programs' compliance with FDA standards

would be substantial.<sup>38</sup> In particular, he highlighted that the significant budget allocated to FDA enforcement and inspection initiatives would be extremely difficult for a state to replicate and for a state budget to absorb. Moreover, despite US buyers initially being able to obtain Canadian medication at a reduced cost, there is no measure preventing a US importer from marking up the price of the medicine and keeping the surplus instead of passing on the savings. In light of these factors, non-US supply chains for medicines pose challenges and might not be justifiable.

### Upshots About Law and Supply Chain Safety

The Drug Supply Chain Security Act (DSCSA),<sup>39</sup> enacted in 2013 and still undergoing implementation, establishes stringent requirements for trading partners to enable the tracking and tracing of prescription drugs from manufacturers to distributors and finally to pharmacies. This system enables regulators and trading partners to successfully thwart the infiltration of counterfeit ingredients and drugs into the drug supply. However, drug importation compromises protections outlined in the DSCSA by allowing foreign prescription drug packages alongside FDA-approved products.

While ensuring access to affordable medications remains a global priority for patients, this objective should never compromise patient safety. Policy decisions related to prescription medications and public health should prioritize drugs' quality, safety, and legitimacy. Drug importation as a policy fails to address the root causes of drug pricing and accessibility in the United States and instead introduces new health risks, which directly contradict the evidence-based approach followed by the FDA and the Department of Health and Human Services since 2000.<sup>40,41</sup> Importing prescription drugs from Canada not only weakens the existing controls in the historically safe pharmaceutical supply chain, but also misleads consumers by wrongly suggesting the safety of drugs sourced from other countries.

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## AMA Journal of Ethics®

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### AMA CODE SAYS

#### AMA Code of Medical Ethics' Opinions Related to Global Medical Supply Chain Security

Maura McGinnity

##### Abstract

Global medical supply chain security is essential for the health care system to run efficiently and allow physicians to effectively treat patients. When the global medical supply chain fails, as was seen during the COVID-19 pandemic, physicians are put in the difficult position of not having enough resources and being required to put themselves at risk to provide care for sick patients. The *AMA Code of Medical Ethics* provides opinions giving guidance to physicians regarding this issue.

##### Introduction

The global medical supply chain is an extensive group of systems and processes that work together to ensure that health care supplies and resources are distributed to health care organizations and hospitals. Providing resources for patients is the main priority in medical supply chains. Three opinions in the *AMA Code of Medical Ethics* are relevant to the ethics of global medical supply chains: Opinion 11.1.3, “Allocating Limited Health Care Resources”<sup>1</sup>; Opinion 8.3, “Physicians’ Responsibilities in Disaster Response and Preparedness”<sup>2</sup>; and Opinion 1.1.6, “Quality.”<sup>3</sup>

##### Resource Allocation

In the midst of a global health crisis, **allocation of resources** is an essential factor in keeping the public safe. During the COVID-19 pandemic, drug shortages and restricted access to personal protective equipment (PPE) put patients and physicians at risk. Opinion 11.1.3 explains that physicians, both individually and collectively, “should advocate for policies and procedures that allocate scarce health care resources fairly among patients.”<sup>1</sup> Opinion 11.1.3 further offers criteria physicians should follow when allocating limited health care resources: “Give first priority to those patients for whom treatment will avoid premature death or extremely poor outcomes, then to patients who will experience the greatest change in quality of life, when there are very substantial differences among patients who need access to the scarce resource(s).”<sup>1</sup>

Accomplishing these ethical duties in the context of a global pandemic requires physicians to adapt quickly to ever-changing circumstances and to evaluate patient needs in relation to the available resources. However, it is important to note the gravity of this responsibility and the implications of these decisions for certain communities.

When global supply chains fail, resources become scarce, and doctors must allocate the limited resources in a way that most benefits patients and public health.

### **Disaster Response and Preparedness Duties**

Physicians and other health care professionals were the frontline workers throughout the COVID-19 pandemic. Due to the lack of PPE and increased number of patients, physicians were placed in dangerous situations in order to care for patients. Opinion 8.3 explains that “[b]ecause of their commitment to care for the sick and injured, individual physicians have an obligation to provide urgent medical care during disasters. This obligation holds even in the face of greater than usual risks to physicians’ own safety, health, or life.”<sup>2</sup>

Opinion 8.3 goes on to explain what physicians should do collectively in disaster response and preparedness:

Provide medical expertise and work with others to develop public health policies that:

- (i) are designed to improve the effectiveness and availability of medical services during a disaster;
- (ii) are based on sound science;
- (iii) are based on respect for patients.<sup>2</sup>

Physicians should also “[a]dvocate for and participate in ethically sound research to inform policy decisions” related to disaster preparedness.<sup>2</sup> During a public health crisis, physicians are on the front line in disaster response. As the global medical supply chains collapsed, the brunt of the failure was felt by physicians and patients.<sup>4</sup>

### **Care Quality**

Providing patients with quality care is of the utmost importance and becomes a prevalent concern when there is a global health crisis and health care systems are overwhelmed. Opinion 1.1.6 specifies that “[i]ndividually and collectively, physicians should actively engage in efforts to improve the quality of health care.”<sup>3</sup> Physicians do so by:

- (a) Keeping current with best care practices and maintaining professional competence.
- (b) Holding themselves accountable to patients, families, and fellow health care professionals for communicating effectively and coordinating care appropriately.
- (c) Using new technologies and innovations that have been demonstrated to improve patient outcomes and experience of care, in keeping with ethics guidance on innovation in clinical practice and stewardship of health care resources.
- (d) Monitoring the quality of care they deliver as individual practitioners – eg, through personal case review and critical self-reflection, peer review, and use of other quality improvement tools.<sup>3</sup>

Opinion 1.1.6 is relevant in the context of global supply chains, as global **medical supply chain security** is essential to patient safety. Supply chains give physicians the resources they need to provide the highest quality care to patients. Specifically, in times of resource scarcity, “keeping current with best care practices”<sup>3</sup> could be based on what is the best care practice during that time, with the resources available. Without secure supply chains in place, there is a high likelihood of failure, especially during public health crises.

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**STATE OF THE ART AND SCIENCE: PEER-REVIEWED ARTICLE**

**Which Data Analytics Tool Should We Use to Evaluate Risk in Upstream Drug Supply Chains?**

Matt Christian, MSc and Wejdan Bagais, MSc

**Abstract**

Drug shortages are a persistent and serious problem in the United States, affecting patient care and health care costs. This article canvasses factors that contribute to drug shortages, such as manufacturing complexity, price, and quality inspection records. This article further proposes an early warning system and payment, contracting, and pricing innovations to mitigate drug shortages and offers data-driven recommendations to stakeholders looking to protect the supply of quality medicines.

**Supply Chain Disruption**

Drug shortages impede health care delivery in the United States, affecting patient care and increasing health care costs.<sup>1,2,3</sup> While the immediate supply chain disruptions triggered by the COVID-19 pandemic are gradually resolving, the United States continues to face persistent drug shortages. In the first quarter of 2023, US active drug shortages were at their highest levels since 2014.<sup>4</sup>

Drug shortages trigger ethical considerations regarding equity of access, information transparency, and crisis management. How should clinicians decide **which patients should have access** to scarce drugs and treatment alternatives? How should drug shortage information be communicated to patients and the public in a manner that is transparent, accurate, and responsible? What are the criteria for evaluating patient demand under crisis conditions?

This article quantitatively evaluates the impact of manufacturing complexity, price, and quality inspection records on drug shortages in the United States using publicly available data from government websites and the subscription-based Medicine Supply Map. By quantifying the factors correlated with drug shortages, stakeholders can make data-driven decisions to protect the supply of quality medicines, ultimately minimizing the ethical dilemmas triggered by drug shortages. Based on our findings, we advocate for the implementation of 2 strategic solutions aimed at fortifying the resilience of pharmaceutical supply chains: (1) investment in an early warning system for drug shortages and (2) exploration of payment, contracting, and pricing innovations

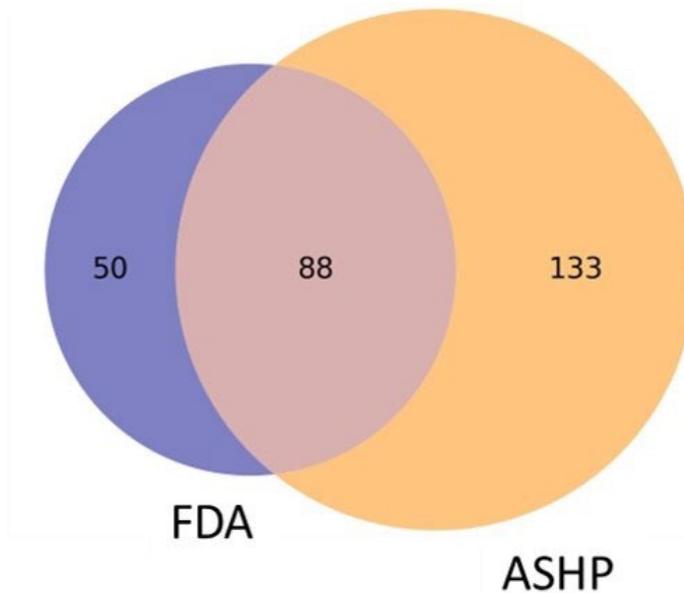
### Defining Drug Shortages in US Markets

Hospital pharmacists receive information about drug supply through wholesalers, manufacturers, and other hospitals, as well as the American Society of Health-System Pharmacists (ASHP) and the US Food and Drug Administration (FDA) shortage websites.<sup>5,6</sup> While both ASHP and FDA report information on drug shortages for US markets, the organizations differ in their definitions and regulatory implications.

The FDA's drug shortage list, managed by FDA drug shortage staff in the Center for Drug Evaluation and Research,<sup>6</sup> focuses on national-level shortages of medically necessary drugs and requires an economic evaluation of manufacturers' ability to supply the market for a given drug product to determine if the drug product is in shortage. According to the FDA website, "We consider a drug to be in shortage when the total supply of all versions of a commercially available product cannot meet the current demand, and a registered alternative manufacturer will not meet the current and/or projected demands for the potentially medically necessary use(s) at the patient level."<sup>7</sup>

ASHP defines a drug shortage more broadly as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent."<sup>8</sup> Because ASHP does not require an economic determination of a national supply-demand imbalance for a drug to be included on the shortage list, as shown in Figure 1, there are more drug products on the ASHP shortage list than the FDA shortage list.

**Figure 1.** Comparison of 271 Drug Products on FDA and ASHP Drug Shortage Lists



Data obtained from the US Food and Drug Administration<sup>5</sup> and the American Society of Health-System Pharmacists<sup>6</sup> on June 26, 2023.

Abbreviations: FDA, Food and Drug Administration; ASHP, American Society of Health-System Pharmacists.

The FDA's drug shortage reporting, unlike ASHP's, triggers certain regulatory actions. When a drug is placed on the FDA's drug shortage list, pursuant to the Drug Quality and Security Act of 2013,<sup>9</sup> certain regulatory restrictions are removed for 503B outsourcing facilities.<sup>10</sup> Such facilities may produce compounded drugs that "are essentially copies

of approved drugs.”<sup>10</sup> Compounded drugs are made by pharmacists according to physicians’ prescriptions but are not FDA-approved and “pose a higher risk to patients ... because they do not undergo the FDA’s premarket review for safety, effectiveness, or quality.”<sup>11</sup> This increased risk to patients is balanced against availability during a drug shortage event. In addition to removing regulatory restrictions for 503B compounding, the FDA can expedite review of manufacturing proposals<sup>12</sup> (eg, changes in manufacturing sites or active pharmaceutical ingredient [API] sourcing), extend the expiry date for certain drug products,<sup>13</sup> and exercise temporary import exceptions to mitigate the impact of drug shortages (eg, the FDA’s temporary import approval for cisplatin from China with non-US labeling<sup>14</sup>).

### **Shortages’ Influence on Health Outcomes**

*Cost of labor.* Hospital systems establish interdisciplinary teams to mitigate the impact of drug shortages.<sup>15</sup> These drug shortage response teams are responsible for determining the organization’s supply forecast, evaluating alternative treatments, and changing patient care processes. Drug shortage response teams must also address ethical considerations related to patient access and patient disclosure, particularly in situations with few or no therapeutic alternatives. The administrative labor cost of managing US drug shortages was estimated to be \$216 million per year in 2011<sup>2</sup> and \$360 million per year in 2019.<sup>3</sup>

*Cost of therapeutic alternatives.* Changing therapeutic solutions to combat drug shortages creates numerous cost, safety, and efficacy concerns. A 2014 study estimated that drug shortages increased health care costs by roughly \$209 million in 2013 due to patients switching to more expensive therapeutic alternatives.<sup>1</sup> Changes to patient care processes, unusual dosing regimens, and worse adverse-effect profiles also increase the risk of medication errors for patients.<sup>16,17</sup>

*Cost to patients and society.* The true magnitude of drug shortages can only be measured through patient and societal impact. For example, the societal cost attributed to elevated mortality rates during the 2011 norepinephrine (a vasopressor used in treating septic shock) shortage has been estimated to be \$13.7 billion.<sup>16</sup> Because **oncology drugs** are inherently difficult to substitute due to their strict dosing regimens, often a shortage of a single drug product will drive supply risk for therapeutic alternative drug products, as in the case of cisplatin and carboplatin.<sup>18,19</sup> As of June 26, 2023, 14 oncology drugs were in shortage, according to the FDA.<sup>6</sup>

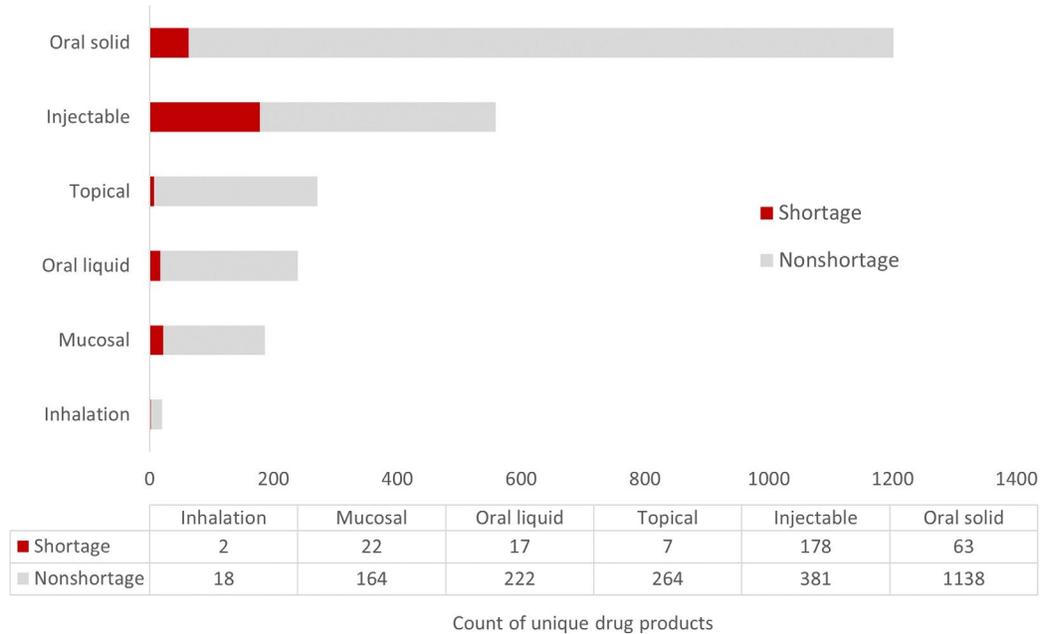
Although a dollar amount cannot be placed on it, the risk of antimicrobial resistance (AMR) due to challenges to antibiotic supply, as exemplified by the recent amoxicillin shortage, also poses costs to patients and society.<sup>20</sup> Effective antibiotic stewardship requires prescribers to issue “the right drug at the right dose at the right time for the right duration.”<sup>21</sup> Switching to a more aggressive antibiotic tier based on supply constraints rather than patient need decreases the long-term efficacy of antibiotic drug products and poses a significant global health concern.<sup>6,22</sup> Additionally, the prevalence of antibiotic drug shortages is intrinsically linked to an increased risk of use of substandard and falsified medicines.<sup>23</sup> Poor-quality antibiotics increase the risk of AMR primarily through the administration of subtherapeutic dosing.<sup>24</sup> Safeguarding the availability of quality antibiotics is thus critical to fighting AMR for patients globally.

### Which Analytics Help Identify Drug Shortage Patterns?

Drug shortages stem from a complex interplay of economic, manufacturing, quality, and geographic factors. United States Pharmacopeia (USP) developed the Medicine Supply Map to identify, characterize, and quantify risks of disruption in the upstream pharmaceutical supply chain. USP identified 3 specific impacts of drug shortages, as defined by drugs' inclusion on either the ASHP's or FDA's drug shortage list, at the drug product level.

*Impact of dosage form on drug shortages.* Injectable drug products are more complicated to manufacture than oral dosage forms. Compatibility studies, sterility assurance, and special handling considerations increase injectables' manufacturing costs and risks of a negative quality event. These factors also increase the risk of a drug shortage. Figure 2 shows that, out of the 559 injectables tracked by the Medicine Supply Map, 178 (31.8%) were in shortage as of June 26, 2023. Rates of shortages are significantly lower for other dosage forms (see Figure 2).

**Figure 2.** Relative Shortage of 2476 Drug Products by Dosage Form



Data obtained from Medicine Supply Map on June 26, 2023.

*Impact of drug product unit prices on injectable drug shortages.* Lower-priced drugs experience more drug shortages, as manufacturers are less incentivized to invest in supply chain resilience. Figure 3 shows the relation between prices and drug product availability.

**Figure 3.** Impact of Unit Price on Supply Chain Vulnerability for Injectable Drug Products



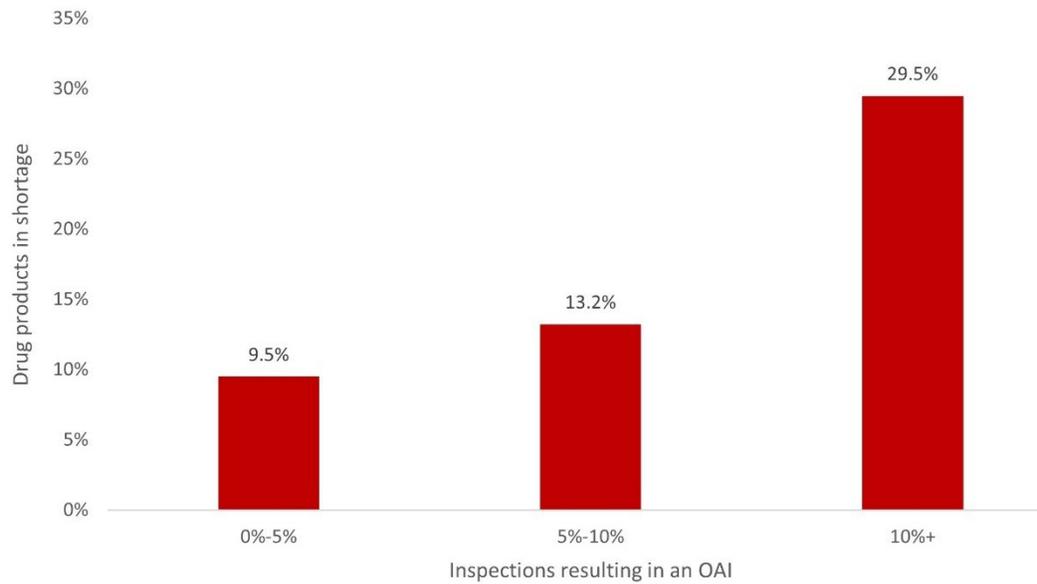
This analysis is based on publicly available pricing data from the US Department of Veterans Affairs<sup>25</sup> and Medicare (Part B and Part D)<sup>26,27</sup> on June 26, 2023.

*Impact of manufacturing quality issues on drug shortages.* Quality issues are correlated with drug shortages. According to the 2019 FDA report on drug shortages, “of 163 drugs that went into shortage between 2013 and 2017, 62 percent went into shortage after supply disruptions occurred that were associated with manufacturing or product quality problems.”<sup>28</sup>

Drug manufacturers are required to test products to ensure that medicines meet the quality specifications approved by the FDA or articulated in a USP quality monograph. The FDA undertook 2442 risk-based drug product and biologics inspections in 2022.<sup>29</sup> FDA inspections serve an important function by helping to protect patients and foster manufacturing quality compliance. Medicines that do not meet quality requirements must be reported to the FDA and withheld from the market.

To quantify the impact of quality issues on drug shortages, the Medicine Supply Map examined the relation between FDA inspection outcomes and drug shortages. We analyzed the proportion of inspections resulting in an official action indicated (OAI) record. The OAI inspection outcome means regulatory or administrative actions are recommended to correct quality issues identified in a manufacturing facility.<sup>30</sup> Figure 4 shows that drug products produced at facilities with a higher portion of OAI inspection records were more likely to be in shortage.

**Figure 4.** Impact of Manufacturing Quality Issues on Supply Chain Vulnerability



Data obtained from Medicine Supply Map on June 26, 2023.  
Abbreviation: OAI, official action indicated.

### Next Steps for Better Analytics and Sharper Surveillance

The journey of a molecule from an API to its final patient destination involves a network of specialized entities. API manufacturers create the primary therapeutic substance, drug product manufacturers transform the API into a consumable medication, distributors and wholesalers transport the drug products, and pharmacies help health care professionals administer medicines to patients. Because pharmaceutical supply chain data are heavily siloed within each specialized entity, solutions to drug shortages must bridge the information gaps across the supply chain. We propose the following solutions to strengthen patient access to quality medicines.

1. *Invest in an early warning system for drug shortages.* Enhancing insight into drug shortages and quantifying the relation between drugs in shortage and explanatory variables can enable stakeholders to make more informed decisions about how to protect patient access to quality medicines. Early warning systems should extend beyond drug product and API manufacturing to key starting materials and excipients to provide a more **comprehensive view of risks** of disruption in the pharmaceutical supply chain landscape.
2. *Explore payment, contracting, and pricing innovations.* Lower prices disincentivize manufacturers from investing in advanced quality systems and supply chain redundancy. A fundamental shift is needed in the market for lower-priced drugs to guarantee more certainty and predictability of both demand and supply and to increase the value placed on a drug's supply chain resiliency and quality in addition to its price. Policy makers and public and private drug purchasers should explore the establishment and utilization of payment, contracting, and purchasing models that value and incentivize drug product quality and supply chain resilience.

## Conclusion

The recent wave of new drug shortages provides the industry with an opportunity to rethink and reshape pharmaceutical supply chains and health care systems. We believe investments in an early warning analytics tool could help industry stakeholders make more informed supply chain decisions. A proactive, strategic, and collaborative approach that incorporates policy, industry, and health care stakeholders could help ensure a stable drug supply and promote better health outcomes for patients.

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## AMA Journal of Ethics®

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### POLICY FORUM: PEER-REVIEWED ARTICLE

#### How Should Resources From National Stockpiles Be Managed?

Geoff Hollett, PhD and Jennie B. Jarrett, PharmD, PhD, MMedEd

##### Abstract

The Strategic National Stockpile (SNS) is a national system maintained by the US federal government to deliver medical supplies during emergencies. In the past, the SNS has been used to mitigate public health consequences of tragedies, such as Hurricane Katrina and Ebola outbreaks. However, challenges in maintaining and utilizing the SNS for patient safety are prevalent. This article canvasses ways in which the SNS is accessed and suggests needed changes in the wake of the COVID-19 pandemic.

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##### Stockpile and Rapid Access

While the concept of stockpiling items in case of an emergency is not new, the Strategic National Stockpile (SNS) is a relatively modern endeavor. In 1999, the US Congress tasked the Centers for Disease Control and Prevention with developing a stockpile of medical supplies for rapid response in the event of a **bioterrorism event**, such as anthrax or tularemia.<sup>1</sup> After the September 11th terrorist attacks, administration of the stockpile was transferred to the Department of Homeland Security before finally being placed under the Department of Health and Human Service's Assistant Secretary for Preparedness and Response. Exact specifications of the SNS are not fully known to the public due to national security implications. It consists of multiple sites in secret locations containing large quantities of medications and medical supplies that can be mobilized and shipped across the country within 12 hours.<sup>2,3</sup>

Although bioterrorism threats have been rare since the inception of the SNS, the SNS has been utilized in other emergency situations. For example, during the H1N1 outbreak of 2009, the SNS deployed over 12.5 million antiviral regimens and nearly 20 million pieces of personal protective equipment (PPE).<sup>4</sup> During the recovery after Hurricane Katrina, the SNS provided 3500 beds, 275 000 vaccines against communicable diseases, and 30 000 vials of insulin to Louisiana and Mississippi.<sup>5</sup> According to a report from the Government Accountability Office, the SNS has received annual appropriations from Congress ranging from \$522 million (FY 2013) to \$845 million (FY 2022).<sup>6</sup> The United States also maintains stockpiles for emergency purposes other than

health care, such as the Strategic Petroleum Reserve, the Northeast Home Heating Oil Reserve, the National Defense Stockpile, and the National Plant Germplasm System.

### Utilization

The appeal of the SNS is clear: rapid delivery of critical supplies in the event of an emergency can be the difference between a minor disturbance and a calamity. In the United States, having the federal government serve as the backstop for national security functions is also crucial in preventing a patchwork of varied state or local plans that may result in vulnerabilities or inequities. In practice, however, the SNS has faced difficulties in executing its core charge. For example, in the emergency response to Hurricane Katrina, one account describes how supplies from the SNS were delivered but went unused due to lack of jurisdictional clarity.<sup>7</sup> During the early days and weeks of the COVID-19 pandemic, the SNS struggled to keep up with the demand for ventilators and PPE during the nationwide emergency, as the SNS was designed and implemented to address localized surge capacity.<sup>8</sup>

An illuminating example of the difficulties of the current national stockpile model is the response to the 2022 outbreak of mpox (formerly known as monkeypox), a viral disease that produces skin lesions and is related to the smallpox virus. In May 2022, the Biden administration stated that vaccines for smallpox were effective against mpox and available for deployment, if necessary.<sup>9</sup> The 2 available vaccines effective against mpox in the SNS were JYNNEOS® and ACAM2000® (a third, unapproved vaccine, Aventis Pasteur Smallpox Vaccine, was also available in the event of a declared emergency if no doses of ACAM2000 were available). However, only JYNNEOS was US Food and Drug Administration (FDA) approved for mpox. ACAM2000 was not approved for mpox due to its more severe side effects, including pain, redness, and even myopericarditis and contraindications in infants and pregnant persons, but it was available via compassionate use programs.<sup>10,11</sup> The SNS had large stores of ACAM2000, but not JYNNEOS. Reporting indicates that the SNS would require 132 million doses of JYNNEOS to maintain a full stock, which would support 66 million patients.<sup>12</sup> Yet, during the mpox outbreak, the SNS only contained approximately 65 000 JYNNEOS doses due to 28 million doses having expired in 2017.<sup>13,14</sup> Of the 65 000 doses, only 56 000 were made available for use, in part because JYNNEOS is also effective against smallpox, which is regarded as a national security threat and thus requires its own stockpile for response.<sup>13</sup>

Health care products, particularly medications and vaccines, are expensive and, as illustrated by the mpox outbreak, also expire, and thus require thoughtful investment in the SNS. Items purchased for the SNS are hopefully never used, yet it takes significant resources to maintain their value for emergency preparedness, given that the value of the product diminishes over time. The problem of resources for the SNS expands, however, when it is contextualized as a piece of the federal budget that supports many important programs in dire need of more funds. Fiscal limitations make the SNS an easy target for diverting funds when any other issue becomes a priority. For example, in 2021, \$2 billion (more than double what had been requested for SNS in the most recent FY) was diverted away from the SNS to fund the response to the humanitarian crisis of unaccompanied minors at the southern border.<sup>12</sup> It should be noted that many other factors can also play a role in the capability of the SNS to acquire additional supplies. For example, if a new or repurposed facility was established to provide surge production during an emergency, there can be significant regulatory oversight from entities, such as the FDA, that impact production.

As a society we are poor at anticipating the future and prioritizing future needs. The SNS was more prepared for an mpox outbreak in 2017, a time in which there were no such outbreaks but much more available vaccine. In terms of epidemiology, nothing radical occurred between 2017 and 2022 that would change our understanding of the risk of an mpox outbreak, but our risk tolerance, amidst competing priorities and limited resources, did change. Even when faced with an *active* mpox emergency, the SNS did not release all its mpox vaccine because of the ever-present, competing risk of a smallpox bioterrorist attack. This predictive **risk assessment**, wherein the larger catastrophic risk of death by smallpox was determined to be greater than the risk of disbursing the vaccine stockpile for rarely fatal mpox, allows for morbidity for the sake of preventing potential future harm. This risk assessment is not an implicit failure of the SNS but rather is illustrative of what a challenging, near-impossible task it is to predict what threats are imminent and then accurately scale the response required in a resource-effective manner.

Finally, there are concerns about access and equity related to the SNS. For example, the fact that there is a higher risk of transmission of mpox in men who have sex with men<sup>15</sup> and that not all of the available vaccine was distributed created a gender-based inequity. During the COVID-19 pandemic, the PPE shortage disproportionately impacted women, as PPE stored in the SNS was ill-fitting and designed for men.<sup>16</sup> The needs of society change over time, and a stockpile and manufacturers of the materials it contains are not necessarily responsive to a change in our understanding of and approach to combating health inequities. Additionally, keeping critical medical supplies in a stockpile may be considered hoarding, and with every medication that expires while sitting on a shelf in the SNS, was there someone in the United States, or even in the world, who needed it?

### **Modernization**

Despite its flaws, the SNS represents a **commitment to emergency preparedness** that cannot be lost moving forward. However, the United States' slow emergence from the COVID-19 pandemic offers an opportunity to reflect on how emergency preparedness may need to be modernized to adapt to the realities of our world. Preemptive purchasing and storage may not be the most effective use of resources if governmental agencies are poor predictors of what needs to be preemptively purchased. Rather, programs that were more successful in responding to recent emergencies were those with greater flexibility, such as drive-through vaccination clinics, which were rapidly established during the COVID-19 pandemic.<sup>17</sup> In an era of 3D printing and additive manufacturing, perhaps a reimagining of the SNS would entail not hoarding of PPE but instead creating dedicated manufacturing sites that could rapidly tailor outputs to the needs of the emergency response, similar to how the Defense Production Act allows the presidential administration to utilize private manufacturing capabilities, as was seen during the COVID-19 response.<sup>18</sup>

This approach is not without its flaws, however. First, disputes over intellectual property would need to be resolved, particularly if the government were to be the one manufacturing a design that is privately owned. Second, it understates the complexity of manufacturing many of the medications kept in the SNS. Is it truly feasible for the government to maintain multiple sites capable of sterile, Good-Manufacturing-Practice compliant, FDA-regulated manufacturing of medications or biologics, such as an mpox vaccine, at a moment's notice? Third, sourcing and stockpiling the requisite precursors and materials needed to facilitate responsive emergency manufacturing would likely run

into all the same issues the SNS faces by stockpiling the final product. Perhaps a more fruitful approach would be to have the SNS serve as a central marketplace for some of its contents that can be bought and sold by states, countries, or private entities, while maintaining the ability to mobilize its stock in the event of an emergency instead of the current model, in which states that wanted to acquire their own supplies were instead outbid by the federal government replenishing the stockpile.<sup>19</sup>

### Conclusion

Two things are simultaneously true about the SNS: it is a key piece of US emergency preparedness, and it may never be able to adequately respond to all emergencies. The strategy of locking medicines away behind closed doors while waiting for their expiration is not responsive to changing demands and will forever require fighting to maintain a stable stream of funding in an era of constantly evolving priorities. Upon the emergence from the greatest global emergency of our lifetimes, there is an opportunity to reflect and to rebuild an emergency preparedness system that is responsive to the system that wants to use it.

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## AMA Journal of Ethics®

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### **POLICY FORUM: PEER-REVIEWED ARTICLE**

## **Surveillance and Security in US Medicine and Equipment Supply Chains**

Mahshid Abir, MD, MSc and Bradley Martin, PhD

### **Abstract**

The COVID-19 pandemic exposed vulnerabilities of the United States' routine and emergency supply chains of medicines and critical equipment. These vulnerabilities underscore an urgent need to prevent routine and emergency shortages by making drug manufacturing more transparent and by tracking how key supplies get to end users. Near real-time surveillance systems must be developed to monitor fluctuations in supplies of medicines and equipment. Implementation of such systems will require getting key stakeholders (clinicians, administrators, community members, manufacturers, and policy makers) to collaborate.

### **You Can't Prevent a Problem if You Can't See It Coming**

Medical supply chains are pertinent not to a single medicine, equipment, or process but to all items and processes needed to care well for a patient. To provide health care, specific products—ranging from testing equipment to disposable supplies and pharmaceuticals—may need to be available to practitioners or patients. Some items may have originated thousands of miles away and crossed many national boundaries to reach the end user. The assessment of medical supply chains and approaches to mitigating disruptions are complicated by the diversity of medical supply chains, which range from highly engineered pharmaceuticals and complicated life support equipment to disposable test kits and generic drugs.

Although the challenges and requirements involved in supply chains related to different products can vary, supply chains develop because manufacturing of different products may be more readily and efficiently conducted in certain places than others. Private interest is an intrinsic part of the reason for development of complex supply chains. Companies seek suppliers that have more direct access to critical components and have a labor market and regulatory environment more favorable to a particular business, and they are principally motivated by what minimizes risk and cost and maximizes profit. As a result of these considerations, medical supply chains have become highly distributed in numerous countries.

### **Routine and Emergency Medicine and Equipment Shortages**

The COVID-19 pandemic drew national attention to the issue of **medical supply shortages** in the United States, evident in shortages of personnel protective equipment

and ventilators in health care facilities across the nation.<sup>1</sup> However, medical supply shortages have been a challenge for hospitals and health systems long before the COVID-19 pandemic. On a routine basis, many critical medical supplies—such as crystalloids, antibiotics, and pain medications—have intermittently been in short supply,<sup>2</sup> putting both health care professionals and patients in a precarious position.

Whether the medical supply shortage is due to decreased production, increased demand, or problems with getting the supply to the end user in the last mile, there may be serious consequences for patients due to delays in treatment or receiving suboptimal care. Substitutes for therapies that are in short supply may not be as effective in treating a patient's condition or may have unintended negative effects on the patient's health outcomes. In many instances, hospitals and health systems do not have the ability to predict potential supply shortages, further complicating their ability to prevent shortages by securing the needed supplies or equipment through alternate suppliers.

Safeguarding medical supply chains is an essential part of ensuring delivery of care,<sup>3</sup> and failure to appropriately safeguard them could be particularly harmful for the most vulnerable. Providing safeguards relies on 3 components:

- *A significantly more complete understanding of supply chains, with particular emphasis on where they might be most vulnerable.* It is not sufficient to assume that industries will take care of the chains because it is in their interest to do so. The parts of interest to companies—which largely revolve around protecting supplies for their particular products—may not be the parts most important to the collective interest. For example, that critical commodities might come from nations hostile to US broader geopolitical interest is not necessarily a matter of concern to companies accustomed to receiving those commodities.
- *An awareness that private-public partnerships are inevitable.* This awareness should be coupled with a clear understanding that partners' incentives and perspectives are different.
- *A firm plan to ensure security of supply chains in the event of emergencies and particularly in times of geopolitical conflict.* We do not advocate this readiness in the spirit of building leverage but in the spirit of ensuring that essential services are continued.

The last mile of delivery refers to the part of the supply chain from a distribution hub to being in the hands of a patient. It is an oft-neglected part of the supply chain but can be as subject to disruption as other parts of the chain thousands of miles away. Labor, transportation, or even jurisdictional issues can occur here as easily as they can at much closer locations.

### **Why Are Chains Opaque?**

The **security of a supply chain** means different things to different actors. Companies providing specific goods and services have supply chains, and their business depends on keeping those secure. Private actors generally will not intentionally put parts of their supply chains in vulnerable areas if they cannot devise a way of coping with potential risk, usually by specifically planning for an alternate source and pricing risk and replacement into the cost of the commodity. If an individual company has the means or interest in overcoming a disruption, it likely will find a way. However, the company is not generally factoring social welfare into its risk decisions. Their supply chain

resilience—or lack of it—may have direct impact on general welfare, but general welfare is not the basis of decision making.

Although it is often true that supply chains secured for a single company or even for a set of companies at least correlate with regional and broader global security, the fact that a company might have what it views as a secure supply chain for a particular period does not mean that a community can be assured of a secure supply across every commodity. Private interest may in fact be best preserved by concealing information, not only from possibly malevolent actors but also from regulators and competitors. The divergence between private and collective interest can become a serious problem for overall supply chain security and thus for delivery of medical services overall. Although there may be value overall in every actor having visibility into supply chain vulnerabilities, to individual companies the benefit might not be clear and indeed might seem to go against their obvious interest. However, there are reasons for private actors to support greater transparency that go beyond their immediate interest. We will consider these in more detail in subsequent sections.

### **Need for Surveillance**

Prediction and prevention of medical supply shortages is critical to mitigating their resultant negative impacts. A 2019 report released by the federal Drug Shortages Task Force called for “adoption of risk management plans to proactively assess risk and to predict and prevent supply disruptions.”<sup>4</sup> Prediction and prevention are predicated on having advance knowledge of potential shortages. Such situational awareness can only be achieved if hospitals and health systems have access to **supply chain data** in near real-time. What are some past and current trends in availability of a supply leading to a shortage? How much of a given critical medical supply from various manufacturers is currently in the market? Where are various medical supplies—and their components—made? This type of information can help communicate the likelihood of potential shortages to health care facilities, allowing them either to prevent a shortage by turning to suppliers more likely to be able to accommodate their needs or to plan for an inevitable shortage by securing alternate therapies.

One example of an existing, near real-time surveillance system in the United States is the Centers for Disease Control and Prevention’s National Notifiable Diseases Surveillance System, which is the basis of publicly available, weekly updated cases of nationally notifiable infectious diseases and conditions reported by every state.<sup>5</sup> A near real-time surveillance system for the US medical supply chain can be built following a similar model. A relatively simple, and immediately feasible, version of this system could include data inputs on available (and optimal levels of) medical supplies and equipment voluntarily entered into the system by hospitals and health systems across the country. Such a system could help medical facilities identify hospitals and health systems that may have a surplus of a given supply and equipment that a facility in need could potentially acquire. Through establishment of memoranda of understanding, hospitals and health systems could be incentivized to participate in such a system as an approach to alleviating future shortages that their organization might face. Participation by hospitals and health systems could also be incentivized through state or federal grants or tax cuts.

A more advanced version of this surveillance system could include information on suppliers—the location of their manufacturing facilities and the source of their supply and equipment components. Such information, monitored by emergency managers or

other designated hospital staff, could cue health care facilities if, and when, the source country for a given medical supply or piece of equipment (or their components) experiences potential interruptions in production due to a natural disaster or sociopolitical unrest, for example.

Such a near real-time medical supply and equipment surveillance system could be used both routinely and during disasters and public health emergencies to gain situational awareness of the resources that exist within the larger US health system and those that exist within the supply chain that could potentially be leveraged to create surge capacity.

### **Transparency Is Surveillance Success**

In order for a near real-time surveillance system to be functional, key stakeholders—whether hospitals and health systems or manufacturers of medical supplies and equipment—need to (a) be willing to share their data for input into the system and (b) have the resources and commitment to update these data on a (near) daily basis. Given that many hospitals and health systems publicly report data on number of beds, available capacity, and costs of medical supplies and equipment, it would seem reasonable to believe that such facilities may be willing to share data concerning their existing medical supplies and equipment.

However, the current (and long-standing) level of opacity concerning where a given product and its components are manufactured makes the inclusion of manufacturer-related data in the surveillance system a major hurdle. Whether the surveillance system is public or only accessible to parties (for example, US government agencies, hospitals, and health systems) on a need-to-know basis, manufacturers of medical supplies and equipment would need to support more transparency concerning their products, where they are produced, and where components are sourced. Given manufacturers' historical resistance to sharing such data, a mix of incentives and disincentives would likely be needed to get manufacturers to share their data.

Legislation that incentivizes medical supply and equipment manufacturers to be more transparent—and to share data—regarding where their products and product components are manufactured is an important step in helping health care facilities have the information they need to predict and mitigate potential shortages. Such incentives could include government grants, subsidies, and tax breaks based on the level of transparency. On the other hand, manufacturers that choose to remain opaque could be subjected to higher taxes.

There are additional hurdles to requiring manufacturers to share data that would facilitate predicting and preventing drug shortages. For example, the US Food and Drug Administration (FDA) cannot ask manufacturers to report an increase in demand for drugs under current laws.<sup>6</sup> On the other hand, under the Safety and Innovation Act, the FDA can require manufacturers to report “supply disruptions, delays, and discontinuations in manufacturing”<sup>6</sup>—which can help inform a medical supply chain surveillance system and facilitate early drug shortage notification.

### **Roles of Health Systems and Public Governance**

Given the long history of lack of transparency in information related to medical supply and equipment manufacturing, much advocacy will likely be needed on the part of health care professionals, patients, and communities. Ultimately, it is the work of health care professionals and the health of their patients that are on the line during medical

supply and equipment shortages. Advocacy by these very stakeholders is critical to getting policy makers to prioritize solutions that encourage manufacturers to be more transparent and to input data in a supply chain surveillance system.

### Next Steps

Realizing a near real-time surveillance system to develop situational awareness of fluctuations in availability of critical medical supplies and equipment will require getting the key stakeholders at the table—including health care professionals and administrators, patients and communities, medical supply and equipment manufacturers, and policy makers. Long before the pandemic, health care facilities routinely experienced shortages in supplies critical to patient care. The COVID-19 pandemic further exposed the vulnerability of the US medical supply chain by introducing a sense of urgency into the issue of increased manufacturing transparency and supply chain data tracking to both prevent shortages and swiftly address them before they occur. Advocates and policy makers should seize this moment to propose legislation that will help secure the US medical supply chain.

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**MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE**

**How Should We Draw on Pharmacists' Expertise to Manage Drug Shortages in Hospitals?**

Michael Ganio, PharmD, MS

**Abstract**

This article argues that drug shortages should be addressed as crises that exacerbate already compromised US health care infrastructure. Clinicians, especially pharmacists, can help limit threats that shortages pose to patients. For example, pharmacists can canvass procurement options, consolidate inventory, and prepare medications to prevent need for some clinical interventions. This article describes how pharmacists' preparation and training equip them to help clinical teams navigate shortages by equitably rationing limited medicines, suggesting appropriate therapeutic alternatives, modifying drug administration routes, or delaying interventions. Pharmacists' roles can be key, since good management of supplies during drug shortages can mitigate risk of worse-than-usual clinical outcomes, mitigate risk of medication errors, and reduce some financial burdens on the overall health care system.

**Falling Short**

Drug shortages have increased since 2007,<sup>1</sup> limiting options for patients and forcing health care practitioners to adapt quickly in order to provide the best care possible. While no therapeutic category or dosage form is immune from the risk of a shortage, the most common shortages affect older, generic, sterile injectable drugs.<sup>1</sup> **Chemotherapy drugs**, antimicrobials, anesthesia agents, nutrition support products, and emergency response drugs have all been affected by severe shortages in the past several years.<sup>1</sup> The ongoing threat that drug shortages pose to our national health care infrastructure has even been considered a risk to our national security.<sup>2</sup>

While there are hundreds of ongoing drug shortages at any given time,<sup>1</sup> there are often strategies practitioners can implement to reduce their impact.<sup>3</sup> When the pharmacy team learns about a drug shortage, it immediately plans how to manage the shortage. By using data on current inventory levels and utilization trends, the team calculates how long the supply on hand will last and begins exploring alternatives while also investigating the cause of the shortage to project its severity and duration. In cases in which the pharmacy can successfully plan ahead and manage inventory, patients and non-pharmacy members of the health care team might not even be aware of the shortage. In other cases, clinicians must make difficult decisions about how a **scarce**

resource must be rationed to ensure equitable use when no acceptable therapeutic alternatives exist.

In general, strategies used to mitigate the impact of drug shortages can be broken down into 2 categories: operational and clinical. Operational changes include procuring drugs from alternative suppliers or from compounding outsourcing facilities, sourcing different vial sizes or concentrations, employing different means of drug preparation in the pharmacy, repackaging larger vials as unit-of-use doses, and updating electronic health records (EHRs), smart infusion pumps, and other health care technologies. Clinical strategies include conversion to other dosage forms (eg, from injection to oral tablet or capsule), conversion to other routes of administration (eg, from small-volume parenteral infusion to intravenous push injection), therapeutic interchange with an alternative drug, or rationing.<sup>3</sup> Many of these changes present ethical challenges, as patients may be put at increased risk of medication error, receive second- or third-line treatment, or have care delayed or canceled.

### **Clinical and Financial Consequences of Drug Shortages**

While any clinician can attest to the impact drug shortages have on daily practice, there is a general lack of comprehensive information about the clinical and financial effects of shortages. Indeed, information that is available may underestimate the true impact.<sup>4</sup> Comparisons of standard-of-care treatments to alternatives implemented in response to a shortage are not common in the medical literature. For example, a 2017 publication reported higher in-hospital mortality among patients with septic shock admitted to hospitals in which use of norepinephrine relative to other vasopressors decreased by at least 20% due to a shortage of norepinephrine.<sup>5</sup> Evidence of harm due to medication errors associated with shortages is more widely available. The Institute for Safe Medication Practices has published reports about deaths and other harms caused by medication errors, substitutions, or omissions associated with drug shortages; 15 deaths in a 15-month period were reported in 2011 and 2012 due to such errors.<sup>6,7</sup> Lesser harms associated with drug shortages are common; in a 2022 American Society of Health-System Pharmacists survey, 7% of respondents reported at least one shortage-related medication safety event that caused at least temporary patient harm.<sup>8</sup> Moreover, numerous cases of adverse events, including deaths, have been reported as a result of compounding errors or contamination during the compounding process.<sup>6,9,10</sup> Organizations performing compounding or using outsourcing facilities should be aware of the risks and ensure that their compounding program or the outsourcing facility is in compliance with applicable standards, laws, and regulatory guidance.

The financial impact of shortages is also difficult to ascertain. Therapeutic alternatives may be more costly than the standard of care. Outsourced compounded products are typically more expensive than their commercially manufactured counterparts.<sup>11</sup> The cost of a drug that has been in short supply can also increase after a shortage, adding to the overall expense of a shortage.<sup>12</sup> From interdisciplinary action plans to inventory movement to bedside care, implementing strategies to manage drug shortages is often labor intensive. A 2019 report estimated that the labor cost of drug shortages is about \$360 million in annual health care expenditures.<sup>13</sup> Given the increasing number of drug shortages and added labor expenses experienced during the COVID-19 pandemic, this number likely underestimates the current cost of managing shortages. The increased **burden on clinicians**—monitoring supply availability, following up with patients, and communicating about preferred alternatives—adds stress to a workforce already challenged by burnout and staffing shortages.

## Operational Strategies

Operational strategies often result in no clinical change to a patient's treatment. Organizations may begin shifting inventory of drugs in short supply to either centralized locations or patient care areas where product may be more urgently needed, or both. Moving product to centralized locations, such as the pharmacy, allows more oversight of rationing and close monitoring of days' supply on hand.

When faced with a shortage, purchasers will also begin exploring alternative products and suppliers. Alternatives can include the same product from a different manufacturer or sourcing from a secondary wholesaler. "Gray market" vendors may also advertise drugs in shortage, but purchasers should be aware of extreme price markups and that counterfeit products can be introduced through the gray market.<sup>14</sup> As discussed below, alternatives can also include compounding or using a different package size, strength, or formulation of the same drug.<sup>8,15,16,17,18</sup>

Compounding options include either preparation in a hospital or health-system pharmacy or buying from a US Food and Drug Administration (FDA)-registered 503B outsourcing facility. Compounding can involve starting with FDA-approved commercial products or starting from nonsterile bulk drug substances, which requires special expertise and compounding conditions. Compounding is not a comprehensive solution to drug shortages, but it is a common strategy to address specific shortages. Outsourcing facilities cannot begin compounding a copy of an FDA-approved commercially available product until it appears on the FDA drug shortage list, which can limit how quickly they can respond.<sup>19</sup> To provide supply of a drug in shortage, outsourcers must find suitable suppliers of bulk ingredients and materials, research a suitable formulation of the drug, conduct stability studies to determine an appropriate expiration date, and complete sterility studies to ensure that the final product is not contaminated.<sup>20</sup> These steps, while important and necessary, can delay the ability of an outsourcer to respond to a shortage. Outsourcing facilities are capable of making thousands of units of drug products but cannot match the millions of units that may be needed to address a shortage of a commercially manufactured product. Rationing and other mitigation strategies may also be required even if a supply of a product is available from an outsourcing facility.

Pharmacies may also prepare drugs differently or source different dosage forms. For example, a hospital may typically purchase premixed infusion bags of a medication, but in the event of a shortage, it may have to prepare doses from bulk vials of medication and individual infusion bags. Pharmacies may also repackage vials or bottles into smaller, unit-of-use doses to prevent waste. For example, during a recent critical shortage of intravenous contrast media, pharmacies had the option of repackaging vials or bottles of contrast into syringes that could optimize supply and **prevent waste** of unused contrast.<sup>21</sup> However, such changes increase the risk of dosing errors. Drug preparation thus should be done in a sterile environment and pharmacy cleanroom to prevent contamination and protect patient safety.<sup>22</sup>

Perhaps most critical to protecting patient safety is coordinating updates within various technologies across the health system. Many hospital health information technology systems, including EHRs, smart infusion pumps, automated dispensing cabinets, and other technologies, include product-specific information such as National Drug Code number, barcode, or other machine-readable coding, as well as package size and

concentration. Whenever changes are made to products, each of these technologies should be reviewed and updated accordingly to ensure seamless transition and reduce the risk of error.<sup>3</sup>

### **Clinical Strategies**

Clinical strategies generally affect the delivery of patient care in some way. In some cases, the patient may receive the same drug but through a different route of administration. Switching from intravenous or other injectable forms of medication to oral doses is common when an oral equivalent is available and clinically appropriate.<sup>15,16,17,18</sup> During the shortage of small-volume saline bags in the wake of Hurricane Maria's destruction of several pharmaceutical manufacturing facilities in Puerto Rico, patients were given oral electrolyte solutions instead of intravenous hydration. In other cases, nurses were asked to stand at the bedside and administer medications diluted in syringes instead of administering drugs using a traditional saline bag and infusion pump.<sup>15</sup>

The more impactful clinical strategies involve therapeutic alternatives, rationing criteria, and even delayed or canceled treatment. Therapeutic alternatives can range from easily substitutable drugs within the same drug class to an entirely different course of chemotherapy, for example. In 2018 and 2019, several blood pressure medications within the angiotensin II receptor blocker (ARB) class were recalled due to nitrosamine impurities found in the tablets.<sup>23</sup> Although there may be pharmacogenomic and insurance coverage considerations,<sup>24,25</sup> transitioning a patient to another drug within the ARB class is not generally a clinically significant change. In 2022, a significant shortage of stimulants used to treat attention-deficit/hyperactivity disorder presented a similar but more difficult challenge,<sup>26</sup> as transitioning between these agents can take time for titration to optimally efficacious dosages.<sup>27</sup> Response and side effects to each drug will vary by individual, making it more difficult to find the best alternative for an individual patient.

Rationing is common in hospitals experiencing shortages of medications<sup>8,15,16,17,18</sup> and involves reserving the medication for a specific indication or patient population with limited therapeutic alternatives. These restrictions can ensure a drug in short supply is available for **patients with the most critical need**. If a patient does not meet the rationing criteria, they may be converted to another dosage form or route of administration of the same drug, or they may be changed to a therapeutic alternative or even nonpharmacological treatment. In the case of chemotherapy shortages, rationing can be especially challenging, as clinicians must decide whether to reduce doses, extend cycle intervals, omit a drug from a regimen, or switch to a less optimal regimen.<sup>28,29</sup> To guide decision making, clinicians and ethicists can evaluate whether treatment has a curative or palliative intent and the expected success of treatment, but, ultimately, some patients will receive suboptimal therapy.<sup>3</sup>

### **Mitigation Solutions**

Drug shortages are a disruptive and costly part of the current health care landscape. They can prevent patient access to optimal treatments and compromise health outcomes by increasing risk of morbidity and mortality. Mitigating strategies include clinical interventions, such as rationing, changing dosage forms, and therapeutic interchanges. Operational strategies include finding alternative sources, using different preparation methods, and compounding. The drug shortage crisis should be considered

a threat to our nation's health care security, and solutions must be implemented to prevent further compromising patient care.

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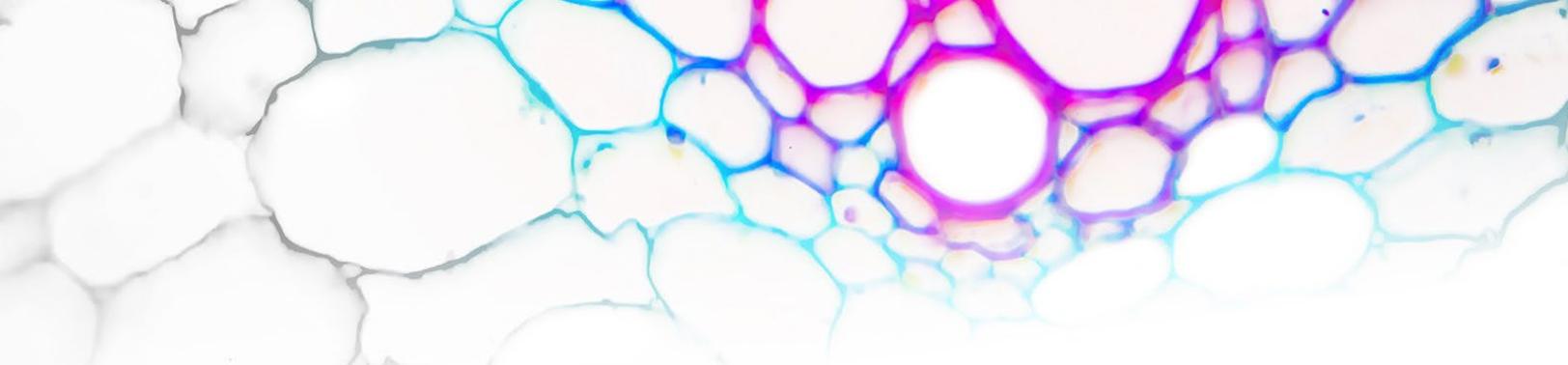
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## MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE

### How Should Critical Medications Be Rationed During Shortages?

Erin R. Fox, PharmD, MHA and Matthew K. Wynia, MD, MPH

#### Abstract

When any drug is in short supply, it must be rationed. Recent increases in the frequency of shortages require more rationing by clinicians. Most health systems have policies on managing drug shortages, but transparency of criteria according to which specific scarce medications should be rationed—and by whom—are rare. The COVID-19 pandemic offered several examples of clinical and ethical need to develop and implement clear, fair strategies for distributing medications in short supply. Lessons from the pandemic should inform strategies for managing drug shortages now and in the future.

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#### Shortages Require Rationing

At the time of this writing, the US Food and Drug Administration (FDA) listed 136 medications in shortage, ranging from inhaled albuterol solution to injectable vecuronium.<sup>1</sup> Even before the pandemic, it was not uncommon to see over a 100 drugs in shortage at any given time, but in recent years the state of drug shortages has become even more severe. Data from the University of Utah and the American Society of Health-System Pharmacists (ASHP) note that the number of ongoing and active shortages in mid-2023 is at a 10-year high.<sup>2,3</sup> Products in short supply today include several standard-of-care chemotherapy agents, critical care medications such as intravenous hydrocortisone, important medications for attention-deficit disorder, and even common medications for diabetes.<sup>2</sup> The most common reasons for drug shortages are quality deficits during manufacturing, as well as economic disincentives to produce low-cost but difficult-to-manufacture products.<sup>4</sup> A comprehensive framework to improve the resilience of the medical product supply chain is available from the National Academies of Sciences, Engineering, and Medicine.<sup>5</sup> But what should organizations do today, assuming shortages will continue to arise and could even become more common and severe?

Most drug shortages are identified by a pharmacy department when an expected order does not arrive. The **pharmacy team** acts quickly to determine how long the stock on hand may last and what alternatives can be purchased. The ASHP Guidelines on

Managing Drug Product Shortages provide comprehensive recommendations and best practices for managing shortages to mitigate patient harm.<sup>6</sup> However, these guidelines cannot help organizations change the fact that when any drug is in short supply, it must be rationed. Some patients will receive it, while others who would otherwise have received it—and potentially derived meaningful benefit from it—will not be able to get it. The cumulative health impacts of all recent or current drug shortages would be challenging to calculate, but in view of how frequently many medications in shortage are used and how effective some of them are in treating common conditions, it is fair to presume that the adverse health effects of having so many drugs in short supply is quite significant. Shortages can also cause patients and caregivers to worry about whether or not they will be able to receive treatment, adding to their stress about their illness.

### **Who Decides?**

Most health systems in the United States have some kind of general policy on how drug shortages are supposed to be managed, but detailed clinical guidance on how to allocate specific scarce medications is often unavailable. Professional societies<sup>7</sup> or federal agencies, such as the Centers for Disease Control and Prevention,<sup>8</sup> sometimes will provide recommendations on how to prioritize patients when a shortage appears likely to last a long time, but this guidance is rarely available at the start of a shortage when initial allocation strategies must be developed and implemented.

This lack of guidance is visible within health systems, where pharmacists are generally at the center of shortage planning but may not directly involve prescribers or others impacted when developing initial rationing strategies. A 2018 survey of 719 health system pharmacists found that all had experienced drug shortages in the last year, with most (69.2%) reporting more than 50 shortages. Some respondents (36%) reported that their hospital had a standing committee to address shortages, but only 13.3% had a committee that included any physicians, and 2.8% had a committee that included an ethicist.<sup>9</sup> Most respondents (92.4%) reported that they typically had less than a month to prepare for an expected shortage, and 81.3% reported that “hoarding” was part of their strategy for addressing incipient shortages. While only about a third of respondents (34.4%) admitted to carrying out overt rationing in the past year, of these, more than half (51.8%) reported that decisions about who would and would not receive the medication were left to treatment teams alone, with no specific guidance, and the remainder (48.2%) reported that committees provided guidance. However, most affected patients (64%) were not informed that their care plans had been altered due to a shortage that required rationing. In short, “who decides” which patients will receive medications that are in short supply varies widely and is rarely guided by careful, transparent, and inclusive deliberation.

Not only are physicians rarely involved in developing specific rationing strategies; many prescribers are unaware when shortages exist. Outside of widely reported shortages during the pandemic, such as **vaccine shortages** in early 2021, inpatient prescribers often become aware that a specific drug is in shortage only when they receive an alert in the electronic health record. In outpatient settings, prescribers may only learn a product is in shortage when a pharmacist notifies them that a prescription they wrote cannot be filled. In some cases, the prescriber might never hear about a shortage affecting their patient if the pharmacist doesn't call and the patient decides not to fill the prescription rather than calling multiple pharmacies to find one with available supply.

In addition, outside of the COVID-19 pandemic, it has been uncommon for health systems to coordinate with each other to better address drug shortages across a state or region. Typically, each system makes its own decisions based on the level of shortage at its own facilities. In fact, in the survey discussed above, 55.4% of pharmacists reported that one of the ways their system coped with shortages was by stopping any sharing of drugs in shortage with other sites.<sup>9</sup> The result is that a drug can be in severe shortage in some organizations but in much better supply in others, often worsening disparities.<sup>10</sup> Recent survey data from the American Society of Health-System Pharmacists demonstrate these differences: of 1123 respondents to a mid-2023 survey of health system pharmacists, 32% said current shortages were severe enough to require “rationing, delaying, or canceling treatments or procedures,” while 63% reported shortages but sufficient supplies to not require rationing.<sup>11</sup> Notably, health systems with better supplies cannot easily share due to provisions in the Federal Drug Supply Chain Security Act that make sending product for more than one patient in emergent need challenging and onerous.<sup>12</sup>

### **Different Decisions**

Given the disparate and often disconnected ways in which rationing decisions are made, it is not surprising that strategies for addressing severe shortages differ in meaningful ways. For example, in the face of a coming shortage, one organization might choose to use its available product as usual until it is gone, while another might stop using it for some indications or groups of patients, seeking to reserve a supply for future patients who might be more likely to benefit. Some might choose to treat only “their” patients and not accept transfers who need access to the treatment in shortage, and some might plan on being able to transfer patients to other systems if they run out of the medication.

Survey data from the early days of remdesivir availability during the SARS-CoV-2 pandemic—when the FDA’s authorization of its emergency use created demand for the drug that was much larger than the available supply—demonstrated this variability in strategies for addressing drug shortages, even as the data also illustrated that most responding organizations took this particular allocation dilemma very seriously.<sup>13</sup> Virtually all responding hospitals (98%) had formed committees to develop criteria for remdesivir allocation, and 94% of those that had done so included adult infectious disease physicians and 35% included ethicists. Yet, even with this level of expertise at the table, hospitals made different rationing decisions. For example, some used a “first come, first served” approach (47%), others used random lottery (22.7%), and a few used comorbidities (4.5%) or essential worker status (4.5%).

### **Equitable Access**

Underlying any ethical rationing strategy is the notion of justice or fairness, although rationing strategies implicitly or explicitly also typically speak to a variety of related values, such as respect for persons, nonmaleficence, community engagement, and equity. For example, in 2012, Rosoff<sup>14</sup> outlined an ethical framework for short-term rationing during drug shortages based on earlier work by Daniels and Sabin and by Hurst and Danis that had laid out general principles for fair allocation of health care resources<sup>15,16</sup>—namely, that strategies for allocating scarce resources should be **transparent and relevant** to the situation at hand and should include both an appeals process and mechanisms for enforcement. Rosoff then added that the process also should not privilege the already-advantaged.<sup>14</sup> Others have argued for even more explicit inclusion of equity in making allocation decisions, and during the pandemic there has

been vigorous debate on whether individual risk factors associated with racial or ethnic background should or should not be included in allocation protocols for ventilators, vaccines, and medications.<sup>17,18</sup>

These debates were spotlighted by extreme racial disparities in access to COVID-19 vaccines when they were in very short supply. Patients with easy access to the internet and reliable transportation, who are often White and wealthy, were far more likely to be successful in accessing vaccines when they first became available. In January 2021 in Dallas County, Texas, for example, non-Hispanic White residents made up “28% of the population but were nearly 63% of those registered to receive vaccinations.”<sup>19</sup> These same patients often were able to obtain therapies when they had been in short supply; they could call pharmacies to ask if nirmatrelvir/ritonavir was available, and they could obtain monoclonal antibody treatments for COVID-19 when access to such treatments often depended on internet access and savvy and time to drive to a center for an infusion.<sup>20</sup> As a result, predictably, there have been large racial disparities in treatment as well as vaccination for COVID-19.<sup>20, 21</sup>

### Strategies for Progress

The COVID-19 pandemic has taught 2 core lessons about how to develop and implement fairer strategies for the allocation of medications in short supply.

First, fair allocation within a community cannot be achieved without a coordinated response across the health care systems serving the community. For instance, during the pandemic, a Utah health system coordinated the allocation of COVID therapies to ensure that patients had an equal chance of access whether they were in a small rural hospital or an academic medical center.<sup>22</sup> Depending on the scale and type of future shortages, national, region-wide, state-wide or city-wide coordination might make the most sense, but having each hospital develop its own plans is a recipe for inequities. Adjustments to the Federal Drug Supply Chain Security Act<sup>12</sup> are needed to allow for easier medication sharing between organizations. New regional structures are being developed that will seek to facilitate regional information sharing and generate uniform clinical guidance to better manage drug shortages.<sup>23</sup> These structures provide a promising avenue for using what we’ve learned during the pandemic to improve how we work together in non-pandemic circumstances to optimize our response to clinically significant shortages.

Second, the pandemic has taught us that strategies for allocating medications in short supply carry a very high risk of not only mirroring underlying **racial disparities** in access to health care in the United States, but also making these disparities worse—sometimes far worse.<sup>20</sup> Consequently, those designing allocation protocols must be attuned to this risk, and they should design allocation strategies to minimize it. They should also plan proactively to track allocation inequities in real time so as to detect any worsening of disparities and be ready to implement additional strategies to mitigate these disparities, such as focusing on efforts to improve access for high-risk communities and individuals.

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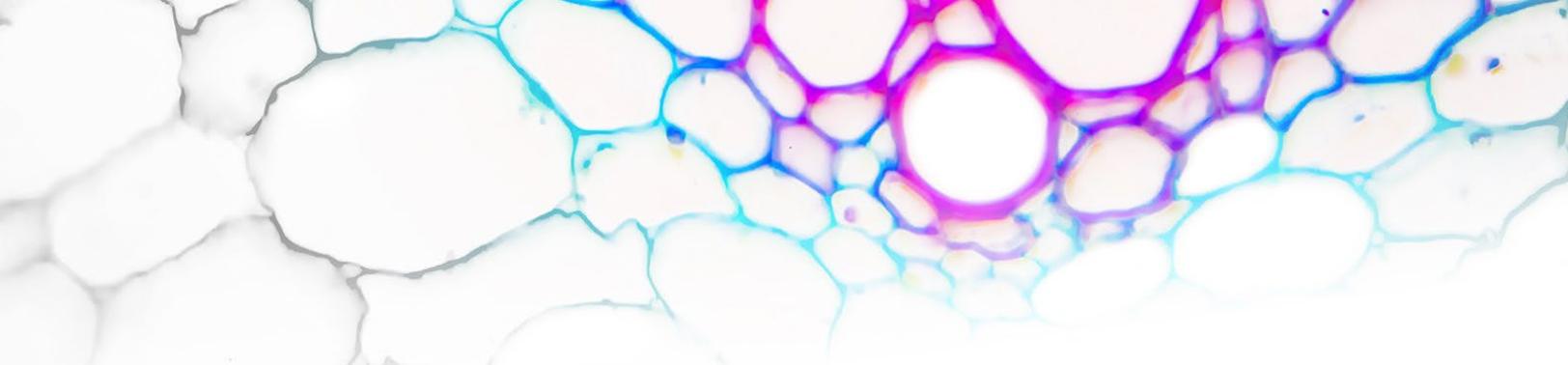
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## MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE

### Mapping a Way to Displaced Persons' Access to Quality Medicines

Carly Ching, PhD and Muhammad H. Zaman, PhD

#### Abstract

Reliable, adequate supply of essential items, including quality-assured medicines, is hard to maintain in refugee camps in low- and middle-income countries. Disruption of medicine supply chains delays treatment for displaced persons and drives procurement of poor-quality products, often from unauthorized or unlicensed sellers. This article explains how current strategies and policies disrupt reliable flow of safe medicines to refugee camps and calls on stakeholders to rigorously map medicine supply chains to refugee camps, which would help identify strategies to improve displaced persons' access to quality-assured medicines.

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#### Refugee Health

Refugee health is a global public health priority.<sup>1,2</sup> The United Nations Refugee Agency (UNHCR) recently reported that, at the end of 2022, there were over 35 million refugees worldwide and over 100 million people forcibly displaced globally.<sup>3</sup> Forcibly displaced communities frequently use health systems with inadequate capacity to diagnose and manage both communicable and noncommunicable illnesses. Additionally, supply of essential items, including quality-assured medicines, has been difficult to maintain in refugee camps, often due to cuts in aid and ongoing conflict and political unrest.<sup>4,5,6,7</sup> Medicine supply chain disruption can result in interrupted treatments of chronic illnesses,<sup>1</sup> irrational medicine usage (especially for communicable diseases), and patients utilizing private, unauthorized, or unlicensed vendors,<sup>7,8,9</sup> who might sell poor-quality medicines or medicines at increased prices.<sup>10</sup> These poor-quality medicines might be substandard—that is, authorized products that fail to meet quality specifications—or falsified by deliberately misrepresenting their identity.<sup>11</sup> Poor-quality medicines can lead to immediate treatment failure or have longer-term consequences, such as antimicrobial resistance development in the case of poor-quality antibiotic usage.<sup>12</sup> Research has shown that poor-quality antimicrobial medicines continue to proliferate in low- and middle-income countries (LMICs),<sup>13</sup> including in and around refugee camps.<sup>14</sup> Procurement and supply of medicines for displaced populations, however, is complex, given constantly evolving environments.

Here, we discuss the risks of poor-quality medicines being procured for refugee camps in LMICs as a result of both regulated and informal procurement strategies and streams. It should be noted that our discussion of refugees might be less applicable to internally displaced persons and urban informal settlements. Awareness of and striving to improve **refugee health** is an important moral imperative for clinicians and health care students, given the increase of conflict and climate change, both of which cause displacement. Because the effects of forced displacement are also global, increased global awareness of complex issues helps prepare health care workers and students to be more empathetic, thoughtful, and better prepared for challenges in caring for diverse communities.

### **How Regulated Medicine Procurement Might Compromise Medicine Quality**

Regulated (official) procurement and distribution of medicines for refugees is generally done via international and local humanitarian organizations and nongovernmental organizations (NGOs). For example, UNHCR uses a competitive bidding process to procure medicines from international vendors, in which requests for bids—typically for a proactive 12-month supply—are posted and different suppliers bid.<sup>15,16</sup> Medicines are purchased using the “best-value quality” criteria.<sup>15</sup> Within this system, **quality assurance** is meant to be built in with certification of the manufacturer’s good manufacturing practices and audits of the supplier’s distribution and storage practices.<sup>15</sup> However, many steps must occur before medicines reach refugees, especially with international procurement. These steps include medicine list and budget approval, quality assurance, preclearance for import, medicine availability, customs, taxes, and having distribution in place, to name a few.<sup>15</sup> As a result, there might be a delay of many months before medicines are received.<sup>16</sup> For example, a medicines shipment was held for 4 months in Jordan because of high customs duty, with the result that the drugs expired.<sup>17</sup> Deterioration of medicine quality can arise from prolonged delays in import or customs clearance, potentially causing extended periods of poor storage conditions (eg, exposure to heat, sunlight, humidity) and consequent expiration of drugs. Additionally, medicine requests are typically based on historical consumption data,<sup>15</sup> which can promote existing patterns of irrational medicine use among refugees.<sup>18,19</sup> Examples include using medicines not prescribed in accordance with clinical guidelines, self-medication (often of prescription-only medicines), and inappropriate use of antimicrobials to treat nonbacterial infections.<sup>18</sup> Once UNHCR procures medicines, they are typically distributed by partners. Importantly, warehouses and storage facilities must have appropriate storage conditions to prevent medicine degradation.

Deviation from procurement policies is sometimes necessary. While it is UNHCR’s policy to bid and purchase medical products through international suppliers to ensure quality,<sup>15</sup> some countries are requiring that medicines be procured locally.<sup>16,20</sup> This policy might decrease lead times, but local regulatory authorities might not be as strict about quality assurance. Many international organizations discourage medicine donations due to concerns about expiration or mishandling. During emergencies, however, there are limited options, and, as such, specific guidelines for donations should be followed.<sup>21</sup> Access to medicines from aid organizations at official organization facilities might also be dependent on legal refugee status.

However, from our correspondence with humanitarian organizations and those who have worked in the field, it emerges that there are often numerous organizations involved in procurement and distribution within a specific camp or geographical area, as well as unauthorized or unlicensed vendors that form informal routes of supply. Thus,

the true nature of the medicine supply chain in refugee camps is not transparent. Furthermore, the role of local governments and national health regulatory authorities, especially in quality assurance, is unclear.

### **Informal Procurement**

While regulated procurement strategies attempt to ensure quality of procured medicines, informal<sup>22</sup> and multiple flows of medicines into refugee camps introduce additional risks of poor quality and irrational consumption (eg, self-medication and misuse of prescription-only medicines). There might be multiple organizations supplying medicines to refugees that do not adhere to strict requirements for international procurement, as do larger NGOs. Moreover, smaller organizations that might have their own warehouses—or use those of larger organizations—to store medicines might fail to follow good storage practices or lack the resources to do so. In addition, some organizations procure specialized medicines or have agreements with local distributors that might procure medicines both internationally and locally, which makes it harder to trace and verify quality assurance. However, local distributors can allow for shorter lead times when more medicines are needed. Officially procured medicines intended for refugees might also be leaked onto the unofficial market.

Medicines can be procured informally in a number of ways. Medicines directly provided by family and friends visiting the camps can enter the supply chain.<sup>6</sup> Within refugee camps, especially long-established camps, there are often unregulated informal pharmacies and outlets. These outlets might carry smuggled medicines or medicines supplied unofficially from local distributors.<sup>8</sup> In instances of conflict, there have even been reports of health care and aid workers teaming up with smugglers to provide needed medical supplies during shortages,<sup>23</sup> which raises the question of whether no medicines or bad medicines is more harmful. Alarming, there are increasing reports of smuggling of controlled substances into refugee camps, putting an already vulnerable population at further risk.<sup>24</sup> Taken together, the medicine supply chain is much more complex than what is defined by documented or regulated procurement practices.

### **Recommendations**

We have a global responsibility to protect refugee health, which includes ensuring supply of and access to quality-assured medicines.<sup>1</sup> To root out medicine quality issues and implement quality assurance along the supply chain and add resilience, we recommend taking the following steps.

*Call for rigorous supply chain mapping in refugee camps.* Given the complex flow of medicines into refugee camps and the lack of accessible information, we call for formal reports that rigorously (quantitatively and qualitatively) map the medicine supply chain in refugee camps to determine and document all inflow channels of medicines, including regulated and informal procurement and distribution and how responsibility is allocated. Such a project might be difficult for academic institutions to undertake alone and will require buy-in and support from governments and international organizations. Due to supply chains' complexity, initial mapping studies would likely focus on specific camps and geographies.

The findings of such a report are critical for identifying problems related to medicine quality and supply and would help strengthen policies for procurement and quality assurance of medicines intended for use in displaced populations. For example, although smuggled or unofficially supplied medicines might raise quality concerns, the

extent of their market share must first be determined. This information can inform strategies to ensure an adequate supply of quality-assured medicines before considering removal of smuggled or unofficially supplied medicines from the supply chain. Data from mapping reports could also be used to implement specific interventions for quality assurance along multiple points and among multiple players within the supply chain, promote increased transparency, and reduce supply chain leaks. The World Health Organization recently commissioned a series of reports on health and migration, highlighting refugee health as an emerging priority area.<sup>2</sup>

*Strengthen local and regional manufacturing to diversify the supply chain.* Procurement by NGOs is largely international due to concerns about limited local manufacturing and quality. Strengthening regional and local manufacturing programs could add resiliency to the supply chain and reduce delays due to transportation and customs clearance, especially during unexpected public health emergencies.<sup>25</sup> Such efforts would require international and local cooperation and continued capital investment, including health systems and regulatory authority strengthening, technical capacity building, and strengthened coupling of regional manufacturing and distribution chains. However, strengthening regional and local manufacturing programs can promote global supply chain resilience, along with human and economic capital development. Challenges of building local manufacturing capacity include not only meeting demand, but also ensuring manufacturers' adherence to international good manufacturing and quality control practices that differ from those of national authorities. Incentives or rewards in the form of a commitment to purchase for ensuring quality and fines for not adhering to quality assurance guidelines might be strategies to build capacity. As it might be difficult for local manufacturers to initially be cost-effective, split tender awards might be a solution. Additionally, factors such as taxation<sup>26</sup> and lead times might be integrated into the best-value quality strategy. Quantifying economic development and benefits such as human capital development that support a higher price premium for quality-assured locally produced medicines might also be necessary.

## Conclusion

Overall, the true nature of the medicine supply chain in refugee camps in LMICs is not well documented, leading to gaps in knowledge about medicine quality, consumption patterns, and refugee health outcomes. While we have focused primarily on the medicine supply chain, effective and rational procurement must be integrated with robust health service delivery that refugees trust. We also note that striking a balance between humanitarian aid to refugees and adequate supply to citizens when medicine shortages might exist for both populations will require further analysis, especially when local governments are involved. Delivering health care and medicines more broadly in **active conflict zones** is another important challenge that requires additional attention and consideration due to the practical realities on the ground. As a global community, we cannot accept refugees' use of inappropriate medicines or medicines of questionable quality and must ensure their access to quality-assured medicines. To do so will require rigorous mapping studies, supply chain strengthening, and coordination between governments and multiple agencies.

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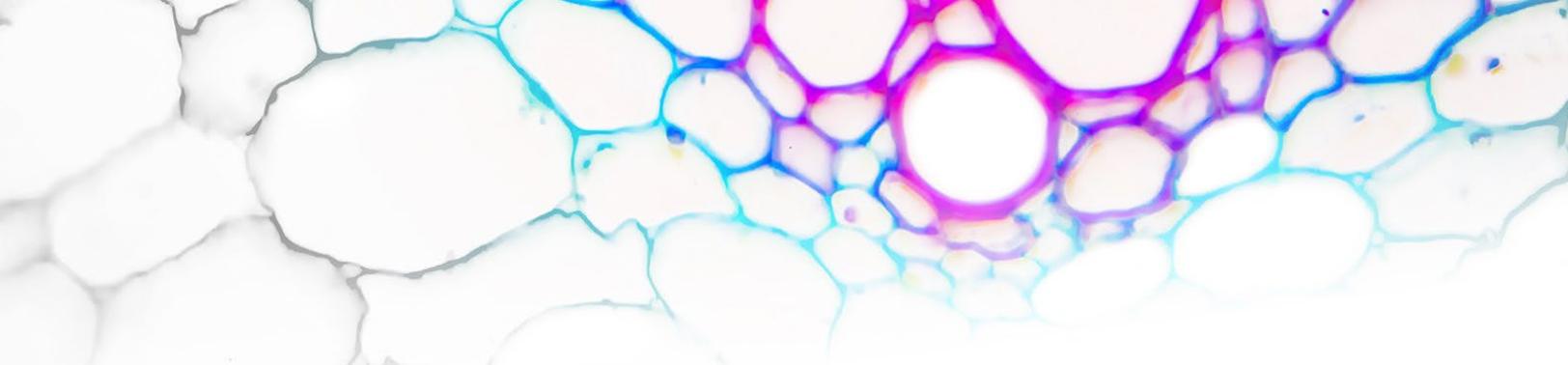
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## AMA Journal of Ethics®

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### MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE

#### How Should Health Care Organizations Limit Roles of Human Trafficking in Their Labor and Supply Chains?

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##### Abstract

There has been little attention given to roles played by human trafficking in health care organizations' supply chains. Hand sanitizers and gloves, for example, might be produced by forced labor, which tends to increase in prevalence during pandemics, mass violence, migration, or other global crises. This article considers the nature and scope of health care organizations' corporate and social responsibilities to procure products and personnel justly, offers recommendations to minimize possibilities that supplies are produced by forced labor, and advocates for a public health approach to limiting human trafficking in organizations' supply chains.

*The American Medical Association designates this journal-based CME activity for a maximum of 1 AMA PRA Category 1 Credit™ available through the AMA Ed Hub™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.*

##### Introduction

Human trafficking is an egregious human rights violation.<sup>1</sup> The United Nations Office on Drugs and Crime defines human trafficking as the act of “recruitment, transportation, transfer, harbouring or receipt of people,” by means of threat or use of force, fraud, or coercion for the purpose of exploitation.<sup>2</sup> The Victims of Trafficking and Violence Protection Act, passed into law in 2000 by the US Congress,<sup>3,4</sup> recognizes 2 different types of human trafficking: sex trafficking and labor trafficking. While sex trafficking can be considered a form of labor trafficking in some contexts, not all labor trafficking includes sexual exploitation. A primary goal of this paper is to call attention to human trafficking in labor and supply chains in health systems; thus, we will be focusing primarily on **labor trafficking**.

For purposes of this paper, labor trafficking or forced labor refers to the trafficking of individuals for forced labor that is not sexual in nature. Worldwide, 27.6 million people in 2021 were in forced labor situations.<sup>5</sup> There are several forms of labor trafficking, including bonded labor, forced labor, and child labor.<sup>6</sup> Victims of labor trafficking can

come from any racial, ethnic, age, gender, religious, or socioeconomic group.<sup>7</sup> However, certain factors make individuals more vulnerable to labor exploitation than others. These include questionable immigration status, language barriers, poverty, and limited social supports, as well as mental health and medical issues.<sup>7</sup> Moreover, forced labor may become more prevalent in times of global crises, such as pandemics, mass violence, or migration, when there may be concomitant acute demands for hospital-based products and staff, as occurred during the COVID-19 pandemic, which exacerbated acute demands for personal protective equipment, masks, gloves, and hand sanitizer.<sup>8</sup> Often described as a form of modern-day slavery, labor trafficking is a fundamental violation of human rights and necessitates a public health response focused on primary and secondary efforts.<sup>9</sup>

Fortunately, recently there have been calls to action for health care professionals to become more educated about human trafficking and its medical, social, and psychological effects on victims and for health care organizations and clinicians to take a more collaborative and interdisciplinary approach to **addressing human trafficking**.<sup>10,11,12</sup> What is less appreciated by health care organizations and professionals are upstream opportunities to prevent human trafficking through thoughtful approaches to both goods purchased and services contracted. Here, we use a human rights lens to highlight the social and corporate responsibility of health care systems in acquiring products. One of our goals for this call to action is to describe ways in which health care leaders can implement solutions to mitigate forced labor and human trafficking risk in logistics and supply chains. Health care workers of all professions and disciplines will want assurance that health care organizations and their leaders are doing everything they can to ensure that any products purchased do not result from forced labor practices.

### **Health Care Organizational Supply Chains**

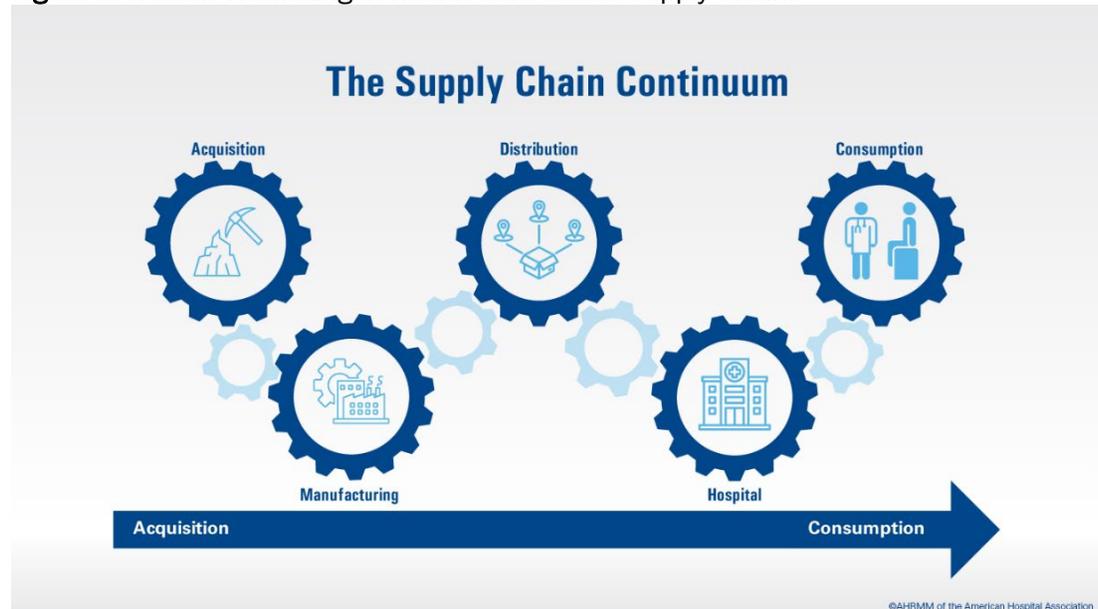
Besides direct service provision to patients, resource procurement can be service- or product-based. Service procurement includes health care workers, building and resource management, food and beverage, housekeeping, and groundskeeping.<sup>13,14</sup> Product procurement involves products, supplies, equipment, and related services and may include the commissioning of the construction or renovation of health facilities.<sup>13</sup>

In 2013, US hospitals spent an average of \$3.8 million on supply expenses, which accounted for approximately 15% of total hospital expenses.<sup>15</sup> Goods supply expenses are the second largest cost category for hospitals after personnel expenses.<sup>16</sup> These figures suggest that health care organizations can have great influence on medical supply companies' hiring and product procurement processes by demanding that the companies that they purchase from adhere to protocols that protect workers' rights and mitigate labor trafficking. Health care organizations could also prioritize partnerships with companies that are located in lower-income countries and that provide safe and healthy working conditions and actively invest in those countries' economies. These kinds of partnerships highlight how the health care industry can influence working conditions and improve the lives of its employees. Health care organizations need vigilance and determination to vet the products used with regard to how they are developed and transported. Ethical product and services sourcing is a social responsibility of health care organizations.<sup>17</sup>

## Oversight

Individuals in the health care and public health (HPH) sector workforce may encounter forced labor at any stage of the supply chain (see Figure 1 and Figure 2). According to the International Labor Organization, indicators of forced labor include deception, restriction of movement, intimidation and threats, retention of identity documents, and debt bondage.<sup>18</sup> HPH organizations may inadvertently facilitate and even benefit from these abuses through product procurement and labor contracting practices.<sup>18</sup> For example, Top Glove, the largest nitrile glove manufacturer, used forced labor practices in Malaysia,<sup>19</sup> and multiple other companies knowingly profited from forced labor in disposable glove factories.<sup>20</sup>

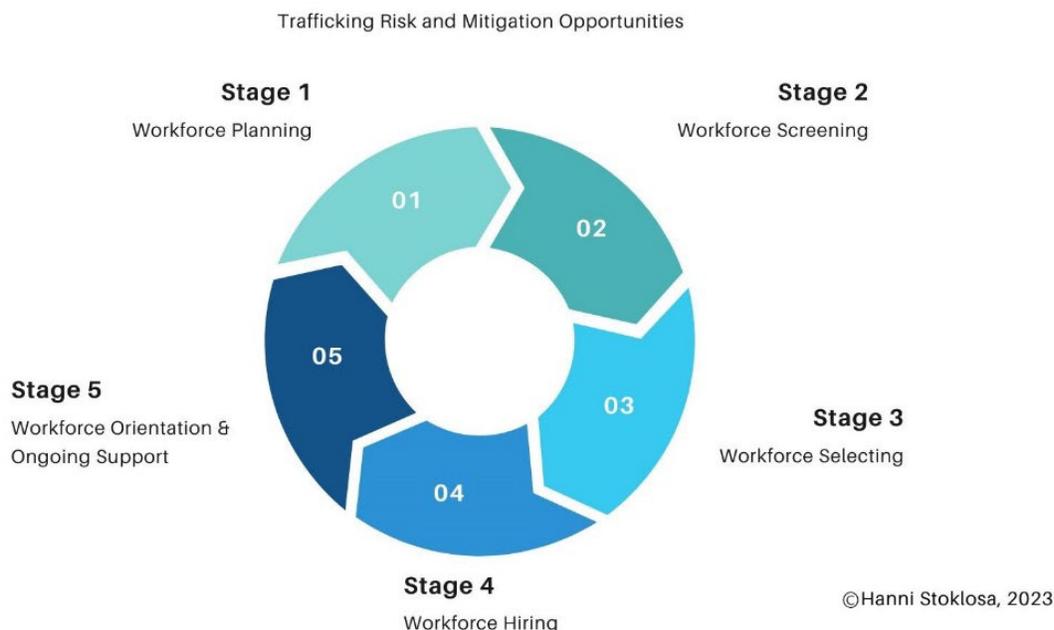
**Figure 1.** Human Trafficking in Health Care Goods Supply Chains



Reproduced with permission of the Association for Health Care Resource and Materials Management of the American Hospital Association.

From left to right, the supply chain involves raw materials acquisition, manufacturing, distribution of the finished good, and point of consumption, which is the health care organization. Human trafficking risk factors follow a similar trajectory, with higher risk occurring upstream at the point of acquisition of raw materials and manufacturing sectors and decreasing risk toward the point-of-consumption side of the spectrum.

**Figure 2. Human Trafficking in Health Care Workforce Supply Chains**



Reproduced with permission of Hanni Stoklosa.  
The workforce supply chain involves stages of workforce planning, screening, selecting, hiring, orientation, and ongoing support. Opportunities to mitigate human trafficking exist at each of these stages.

International and national governing bodies have issued guidance on prevention of forced labor. The Palermo Protocol is the basis for the United Nations Guiding Principles on Business and Human Rights, which instructs companies to utilize principles to identify risks and salient human rights issues in supply chains.<sup>21</sup> In July 2021, the US Department of Health and Human Services published the National Strategy for a Resilient Public Health Supply Chain in response to Executive Order 14001.<sup>22</sup> It reinforces a commitment to an ethical, equitable, and environmentally sustainable public health supply chain. This strategy includes a call for “having processes in place to identify and mitigate sourcing risks such as child labor, forced labor, and human trafficking.”<sup>22</sup> Finally, as the largest government agency in the world dedicated to improving global working conditions and countering labor abuses, the Bureau of International Labor Affairs is uniquely positioned to address labor abuses in supply chains. There are known goods that are produced by child labor or forced labor globally. For example, hand sanitizers are made with sugarcane, and certain countries may use child labor in their production.<sup>13,23</sup> However, banning trade from regions that use child labor does not solve the problem of forced labor in those industries, as poverty and unethical labor practices could increase if one particular trade route is shut off without a mitigation strategy for the forced labor practices.

Since supply chains include workforces at every level, health care organizations should focus on their hiring and employment policies to mitigate the impact of human trafficking. For instance, from the manufacturing to distribution of pharmaceuticals, recruitment of employees should be transparent and lack indications of forced labor, such as withholding passport or visa access. Lower-status workers are particularly vulnerable to labor abuses, and health care organizations may be complicit in the use of this forced labor because they benefit from it. The National Human Trafficking Hotline

has documented cases of health care's role in labor trafficking in hospitals, clinics, and residential care facilities.<sup>14</sup>

### **Health Sector Activism**

*Other industries.* Other industries dedicated to the fight against human trafficking—from which health care industries can learn—include the hospitality, energy, and trucking industries. These industries have identified and responded to trafficking as it interfaces with employee contact with trafficked persons within direct service provision. Additionally, they have developed strategies to address trafficking in their supply chain across all sector areas even when not directly overseeing aspects of their supply chain. For example, Marriott and Hilton conduct diligence checks and third-party certifications as well as audit reports for their suppliers.<sup>23,24</sup> They have also instituted guidelines that hold suppliers to banning forced labor, and regional teams intervene if forced labor is identified or suspected.<sup>24,25</sup> Moreover, the Truckers Against Trafficking and the Oil and Gas Trafficking Awareness Group partnered to create trainings for the over 6 million workers in the US energy sector.<sup>26</sup>

*Health care organizations.* Hospitals—even public ones—are similar to corporations in offering services, and they should be socially responsible for how these services are provided.<sup>27</sup> Ninety percent of the companies included in the S&P 500® Index publish corporate social responsibility reports.<sup>28</sup> Hospitals are remiss if they do not conduct their own social responsibility auditing, even if they choose not to publicize the results. Hospitals can work closely with their suppliers and service providers, distributors, and group purchasing organizations to incorporate contract language and audit processes to identify **risks of human trafficking** within their individual and collective supply chains. Health care organizations may be vulnerable to civil liability claims when they knowingly benefit financially from trafficking in their products. State consumer protection laws arise in class action contexts, highlighting what disclosures or representations companies have made about ethical sourcing practices. The Alien Tort Claims Act gives US federal district courts jurisdiction over civil suits involving violations of international law, including offshore labor practices.<sup>6,29</sup> Corporations, including health care organizations, which have actual or constructive knowledge of trafficking in their supply chains—and, despite having policies and procedures in place, failed to act to mitigate risk—could be held liable for violations.<sup>30</sup>

### **Awareness, Education and Action**

A core tenet of social responsibility is proactive action. Instead of waiting for allegations of forced labor in the supply chain to surface, industries should adopt a forward-thinking mindset to drive everyday decisions.<sup>31</sup> Modern solutions to supply chain risks could include implementing artificial intelligence technologies such as ChatGPT to track sources of materials in supply chains.<sup>32,33</sup>

We recommend the following practices for health care organizations to mitigate the possibility that the products that they use result from human trafficking practices.

- First, health care organizations should aim to have supplier partners participate in a code of conduct provision that confirms no labor trafficking in their manufacturing or among their personnel. This code of conduct provision should include recruitment and retention of personnel in a noncoercive manner.

- Second, health care organizations need to raise awareness of—and use existing tools or resources in supply chains that can mitigate—trafficking risk and ensure the safe and fair treatment of their workers. Resource partners include manufacturers, group purchasing organizations, distributors, and federal agencies.
- Third, health care organizations should develop a compliance program to make sure there is no forced labor in their supply chain. Health care organizations need safe reporting options to raise concerns about illegal labor practices in their services supply chains without risk of retaliation. We encourage health care organizations to create an environment where their employees feel empowered to create changes on organizational, as well as personal, levels. For instance, individual actions such as **reducing hospital waste** can lead to less demand for hospital supplies downstream and less pressure on health care organizations' search for the lowest bids on supplies that may involve unethical practices.

With these recommendations, we advocate for a public health approach to human trafficking risks in health care organizations' supply chains. This approach would build the resilience of health care organizations, raise awareness of trafficking risk, and help prevent continuation of forced labor. These recommendations are crucial to ensuring the safe operation of health care organizations, given the current scourge of human trafficking and the need to ensure medical supplies do not result from—and medical workforces do not comprise—forced labor.

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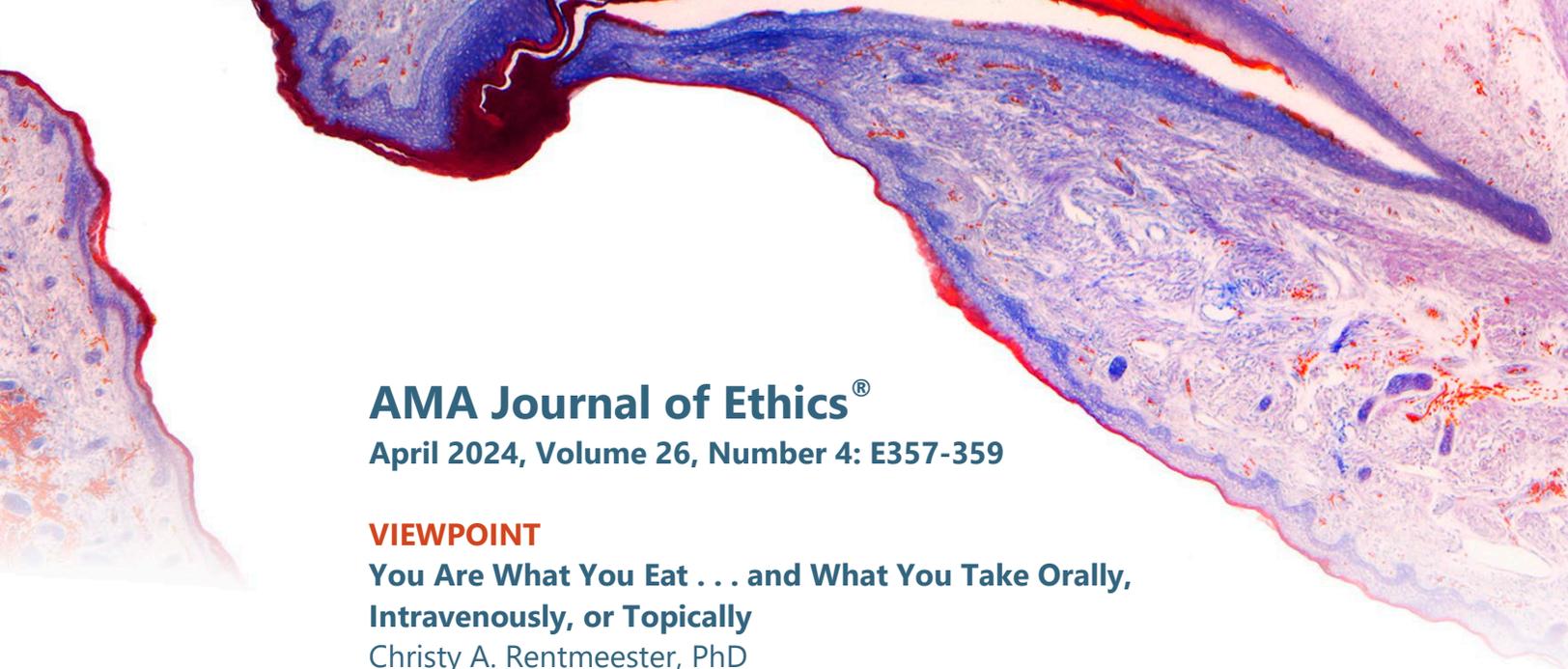
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### VIEWPOINT

## You Are What You Eat . . . and What You Take Orally, Intravenously, or Topically

Christy A. Rentmeester, PhD

### Abstract

This brief suggests a few ethical reasons to interrogate our bioproduct supply chains as we have begun interrogating our food chains.

### Bioprospecting and Biopiracy

Numerous articles since the early 2000s offer distinctions between *bioprospecting* and *biopiracy*. Bioprospecting characterizes practices of identifying what I'll call, for the purposes of this article, *bioproducts* (eg, flowers, trees, fungi, nonhuman animals, these organisms' metabolites or other byproducts,<sup>1</sup> polysaccharides, or cell walls<sup>2</sup>) in order to try to harvest them to generate commercial applications, including in health care. Biopiracy characterizes bioprospecting that happens without profit sharing with communities whose material and epistemic resources have been taken.<sup>3</sup>

Indigenous knowledge about how to apply bioproducts to healing, when taken without acknowledgement, credit, or profit sharing, is a kind of colonial epistemic biopiracy that deserves more thoroughgoing attention from bioethics. Medicinal ethnobotany<sup>4</sup> is a field investigating what Indigenous healers have long known about some plants' addictive properties,<sup>5</sup> for example. We also now know that the source of many compounds now considered "essential medicines"<sup>6</sup> is one single life-giving entity; perhaps we have too long taken for granted the clinical applications of bioproducts<sup>7</sup> that grow on, in, or arise from our common ground, the earth's crust.

### Consumption and Character

An ethical upshot here is that we tend to think about critical **medicine supply chains** in terms of manufacturing, regulation, and transportation. We tend not to ask about how we transform endemic bioproducts (and the landscapes of their origins) in agribusiness practices (good, bad, or neutral) or about how we've normalized and commodified our taking and making of these bioproducts. A point of this essay is to suggest the importance of asking questions such as this one: *What do bioproduction and its attendant agribusiness practices express about our characters—as clinicians, patients, caregivers, consumers—if bioprospecting is rarely, if ever, separable from biopiracy?*

In recent years, we have started to pay closer ethical attention to and ask critical questions about our foods' origins, our agribusiness practices, and what they suggest

about who we are when we eat in certain ways. Michael Pollan,<sup>8</sup> for example, traces a few meals back to their days as photosynthesizers. It is time for bioethics to lead similar investigations into the origins of bioproducts and agribusiness practices that generate many of our medicines, how they're sourced, and who has the most to gain or lose by taking and making them as we do. Probing bioproducts' sources as we have begun [probing how our foods are sourced](#) would likely illuminate distinctions between good and bad actors in industrial bioprospecting. Interrogating our practices of consuming medicines that are bioproducts has at least as much value to our characters as interrogating how we source our foods.

To say that *we are what we eat* is to suggest that our characters are importantly inhabited, dependent upon, and situated by habits of industrialization and consumption we endorse when we grow, market, purchase, and prepare foods. Ways we source medicines, especially from bioproducts, also compose our characters, inhabit who we are physically and ethically, and express how seriously we regard our roles as civic, environmental, and commercial stewards. Thinking more deeply about how we source medicinal bioproducts gives us opportunities to consider whether and how we can or should source them more justly, and not just to avoid the vices of being biopirates.

If health equity is to be more than a trend, bioethics must more deeply investigate the nature and scope of our individual and collective characterological needs to at least mitigate our domestic and international participation in agribusiness practices (eg, unsustainable land use decisions, epistemic theft) that incur costs to and pose risks to some of us when others of us derive inequitable health benefits over the short- or long-term.

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