

## Drug Shortages: The View Across an Ocean

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Drug shortages are a national tragedy and represent a true public health crisis. Drug shortages prevent patients from accessing lifesaving medications and are directly linked to medication errors, substantial economic cost, inferior patient outcomes, and even patient deaths.<sup>1</sup> The recent vincristine shortage, a chemotherapeutic utilized by nearly every child with cancer and by countless adults, represents what one of us has called, “a nightmare situation.”<sup>2</sup> There is no substitute or alternative for vincristine. Confronted with the vincristine shortage, US oncologists collectively hyperventilated with the expectation of looking patients in the eye, conveying that a potentially lifesaving drug is simply unavailable.<sup>3</sup>

Vincristine is not expensive – in most of the world, it costs less than a carton of eggs. It is not new or exotic – isolated during the Cold War, it is readily synthesized. And its efficacy is proven – it is a component of dozens of oncologic regimens. In fact, vincristine is a World Health Organization essential medicine. So how can the US simply run out?

Drug shortages represent a symptom of our inherently damaged healthcare system.

Pharmaceutical companies are responsible to their shareholders; when products are not profitable, through the fault of the marketplace, they are deprioritized. These negative externalities of our current governance structure can only be fixed with legislative sea change.

We briefly review how we got here and suggest how we can move forward.

In February 2018, vincristine, a generic medication for many FDA-approved cancer indications, became scarce. At the time, vincristine was manufactured by Pfizer and Teva. Patients, clinicians, and hospitals struggled to cope with this shortage and breathed a collective sigh of relief once production and supply resumed. With little warning, in July 2019, Teva made a business decision to discontinue production, leaving the US with only one producer of this critical medication required by scores of patients. In October 2019, Pfizer experienced manufacturing delays and increased demand, resulting in a national vincristine shortage. As a result, hospitals and clinicians (once again) faced the unenviable task of rationing this lifesaving medication among equally deserving patients. While clinicians and hospitals will invariably make rationing decisions differently, guidelines for pediatric cancer do exist<sup>4</sup>. These are based upon a 2-step process: step 1 includes strategies to *mitigate* an existing shortage based upon maximizing efficiency and minimizing waste while step 2 elucidates actual *prioritization* grounded upon a modified utilitarian model that maximizes benefit according to total lives saved / life-years saved. Although the focus of the guidance is childhood cancer, the ethical reasoning for explicit decision-making in the face of an actual drug shortage applies broadly to pediatrics and adult medicine in general.

There is simply not enough profit in the production of many cheap, proven, decades-old generic medications like vincristine. Teva is not nefarious – it is a company that needed to shave its

inventory to stay solvent. As appreciated by countless experts, including pharmaceutical insiders, scholars, and the FDA, economics are the primary driver of US drug shortages.<sup>1</sup> The issue involves how drug prices are set and reimbursed in our fundamentally broken system. For this reason, vincristine is only one of *hundreds* of scarce drugs each year in this country.

Institutions are forced to develop ethically appropriate, transparent evidence-guided rationing schema, while expending extraordinary efforts to conserve and procure supplies of drugs on shortage. Rosovsky et al provide a detailed description of their institutional response to the recent heparin shortage, illustrating the magnitude of deliberation and person-hours necessary to create system-level changes to protect patients in the face of a crisis [in press, *The Oncologist*]. The role of ethicists in anticipating and responding to these situations is also critically important.

Institutions would greatly benefit from improved communication and a coordination strategy with regional and statewide partners facing similar circumstances – while Rosovsky’s article is timely and of significant value, we are sure many hospitals across the country would have appreciated being able to better share information and best practices in real time. Unfortunately, despite calls for such a system, currently no structure exists to do so.

We have made some progress. The 2012 FDA Safety and Innovation Act (FDASIA) requires manufacturers to notify FDA of anticipated supply delays and shortages, avails foreign drug

supplies in certain dire situations, and empowered FDA to develop a related strategic plan. Yet, at best, FDASIA was a Band-Aid.

Last month, FDA released a long-anticipated report that summarized and contextualized the current state of US drug shortages.<sup>1</sup> Their recommendations include creating a shared understanding of impact, developing a rating system to incentivize consistent production and to encourage viable contracts with industry. At least some of these proposals are built into the 2020 congressional budget proposal. Notably, many of these recommendations had previously been articulated.<sup>5</sup>

Although realistic, one cannot but be dismayed by the FDA report's concluding statement, "it is likely that drug shortages will continue to persist absent major changes to this marketplace."<sup>1</sup> Herein lies a missed opportunity. A recommendation for greater direct governmental involvement could have, and arguably, should have, been suggested. As one of us recently noted, "The government has previously stepped into the marketplace to assist the ailing automotive industry, Wall Street, and the insurance companies. Why not do the same for our ailing healthcare system, specifically, the manner in which lifesaving medications are manufactured and distributed?"<sup>6</sup> -The government could identify a willing and capable partner with whom to ally to produce affordable and accessible medications reimbursed at a fair

price. Related, “essential medications must be viewed as critical infrastructure not unlike public utilities such as electricity and water.”<sup>6</sup> Doing so is one way to guarantee continuous production and availability for patients in need.

Since the 1970s, international guidance on drugs deemed most critical to maintain has existed. The WHO maintains an updated list of essential medicines nations should readily have. The list is thoughtfully curated based upon data-driven efficacy, relevance, and cost-effectiveness. At the very least, our federal government can and should incentivize production of these drugs, and ideally, in a nation of our wealth and privilege, expand upon it. Earlier this year, a US list of essential medicines for childhood cancer, including recommendations for assuring production of these medications was proposed.<sup>7</sup>

A new European consortium, the International Horizon Scanning Initiative, provides a compelling paragon.<sup>8</sup> Last month, Dutch Minister Bruins announced a novel strategic alignment of nine countries focused on drug pricing, delivery, and supply. This type of collaboration and communication is critical to integrating and creating systems that can readily avail access, and incentivize production for needed drugs, rather than only those that are currently lucrative. America sorely needs to take a similarly bold and creative step.

Drug shortages represent a threat to national security. The US drug supply is overly-dependent on foreign powers; nearly 90% of the raw ingredients we rely upon for US drugs come from China and India while more than 25% of medications labeled as, “made in the America,” are actually made abroad in FDA-inspected plants.<sup>9</sup> This has significant implications regarding medication quality, safety, and accessibility. We currently rely on foreign powers to bail us out when our system cannot take care of our own citizens. America has the capacity and ability to not only provide healthcare to its citizens, but across the world, and a proud history of doing just that. We need to do at least as well for our own people.

Over the past months, there appears to be renewed interest in addressing US drug shortages. The same day the FDA Report was released, U.S. Senators Collins of Maine and Smith of Minnesota, introduced a bipartisan bill coined the *Mitigating Emergency Drug Shortages (MEDS) Act* aimed to increase accessibility and affordability of vital drugs required by patients. The United States Senate Homeland Security and Governmental Affairs Committee also produced a report, “A Price Too High: Cost, Supply, and Security Threats to Affordable Prescription Drugs,” with tangible and actionable solutions<sup>10</sup>. Furthermore, on November 13, Teva USA announced their plan to re-introduce vincristine to the US market as early in 2020 as possible.<sup>11</sup> We are hopeful that meaningful strides will come from these and related efforts.

In summary, our country's perverse drug pricing system creates drug shortages that threaten the lives of the most vulnerable Americans, including, children with cancer. We need federal legislation to ensure that patients in need are able to access essential medications. International precedents and lessons organized by WHO and recently spearheaded in Europe exist. Americans need and deserve access to lifesaving medications, which will require lawmakers and regulators to coordinate and act. Patients' lives depend upon it.



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