

# Chemotherapy Drug Shortages in Pediatric Oncology: A Consensus Statement

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## abstract



Shortages of essential drugs, including critical chemotherapy drugs, have become commonplace. Drug shortages cost significant time and financial resources, lead to adverse patient outcomes, delay clinical trials, and pose significant ethical challenges. Pediatric oncology is particularly susceptible to drug shortages, presenting an opportunity to examine these ethical issues and provide recommendations for preventing and alleviating shortages. We convened the Working Group on Chemotherapy Drug Shortages in Pediatric Oncology (WG) and developed consensus on the core ethical values and practical actions necessary for a coordinated response to the problem of shortages by institutions, agencies, and other stakeholders. The interdisciplinary and multiinstitutional WG included practicing pediatric hematologist-oncologists, nurses, hospital pharmacists, bioethicists, experts in emergency management and public policy, legal scholars, patient/family advocates, and leaders of relevant professional societies and organizations. The WG endorsed 2 core ethical values: maximizing the potential benefits of effective drugs and ensuring equitable access. From these, we developed 6 recommendations: (1) supporting national policies to prevent shortages, (2) optimizing use of drug supplies, (3) giving equal priority to evidence-based uses of drugs whether they occur within or outside clinical trials, (4) developing an improved clearinghouse for sharing drug shortage information, (5) exploring the sharing of drug supplies among institutions, and (6) developing proactive stakeholder engagement strategies to facilitate prevention and management of shortages. Each recommendation includes an ethical rationale, action items, and barriers that must be overcome. Implemented together, they provide a blueprint for effective and ethical management of drug shortages in pediatric oncology and beyond. *Pediatrics* 2014;133:e716–e724

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### KEY WORDS

antineoplastic agents/supply and distribution, resource allocation, health care rationing, ethics, medical, bioethics, coordination, pediatric oncology

### ABBREVIATIONS

ASHP—American Society of Health-System Pharmacists  
COG—Children's Oncology Group  
FDA—Food and Drug Administration  
FDASIA—FDA Safety and Innovation Act of 2012  
WG—Working Group on Chemotherapy Drug Shortages in Pediatric Oncology

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From 2005 to 2011, the number of drug shortages in the United States nearly quadrupled to include >250 drugs.<sup>1</sup> Most involved sterile injectable drugs, including generic chemotherapeutic agents, antibiotics, intravenous nutrition, anesthetics, and sedatives. Shortages of critical drugs are likely to continue for multiple reasons, including unreliable or uncertain sources of raw materials, manufacturing quality problems, regulatory actions, limited economic incentives for generic drug production, and increased consumer demand.<sup>2-4</sup> Emerging evidence suggests that shortages have resulted in adverse patient outcomes,<sup>5</sup> some related to use of substitute therapies,<sup>6,7</sup> and delayed clinical trials.<sup>8</sup> Managing shortages costs valuable time and resources, with annual estimates as high as \$416 million.<sup>9-11</sup> Drug shortages also raise ethical issues: most notably, ensuring a fair distribution of available supplies.

The impact of shortages on pediatric oncology is particularly evident. Many affected drugs are generics, sourced or manufactured by single companies with limited manufacturing redundancy, that comprise the backbones of standard chemotherapeutic regimens.<sup>12</sup> These regimens are potentially curative, and effective alternatives are frequently unavailable.<sup>13</sup> Over the past 10 years, 8 of the 10 drugs used in treating the most common childhood cancer, acute lymphoblastic leukemia, were temporarily unavailable.<sup>14</sup> These drugs account for the 90% 5-year event-free survival of the 3000 US children afflicted each year.<sup>15</sup> Compared with other specialties, childhood cancer therapies are characterized by greater reliance on generic, sterile injectable agents, smaller markets, and unparalleled integration with research via the Children's Oncology Group (COG), other research consortia, and institutional trials. For >50 years, cooperative clinical trials have advanced outcomes in pediatric cancer; historically,

nearly two-thirds of children have enrolled in a trial during their treatment.<sup>16</sup> Although this cooperative context poses special ethical challenges (eg, whether children participating in research should receive priority access to scarce drugs), it may also facilitate potential solutions.

## METHODS

In response to a charge from the leadership of the COG, and with the support of the Johns Hopkins Berman Institute of Bioethics, the authors (the "steering committee") convened a 1-day Working Group on Chemotherapy Drug Shortages in Pediatric Oncology (WG) in January 2013. The interdisciplinary and multiinstitutional WG included practicing pediatric hematologist-oncologists, nurses, hospital pharmacists, bioethicists, experts in emergency management and public policy, legal scholars, patient/family advocates, and leaders of COG and the American Society of Pediatric Hematology/Oncology (see Acknowledgments). WG members were identified by their expertise and national leadership in pediatrics, drug shortages, health policy, and/or bioethics. Before the meeting, the steering committee reviewed the literature on drug shortages, identified 127 articles in ETHXWeb and PubMed published between 1985 and 2012, and distributed an annotated bibliography of the 55 most relevant articles to the WG. The steering committee charged the WG with 2 tasks. The first task was to define the ethical challenges raised by managing pediatric oncology drug shortages within individual institutions. Recognizing substantial previous work on this aim,<sup>17-20</sup> the WG's second aim (reported here) focused on how stakeholders might coordinate efforts related to drug shortages. The steering committee synthesized recommendations from the face-to-face meeting and iteratively circulated these to the WG for comment,

modification, and approval. Here we describe the steps that stakeholders can take, working collaboratively, to prevent and mitigate drug shortages, along with the ethical rationales for and potential barriers to those steps. Although the present recommendations focus on childhood cancer, they require coordination and integration with pediatric and adult specialties beyond pediatric oncology.

## RECOMMENDATIONS

The obligation to prevent and to manage drug shortages is based on 2 fundamental values: the need to maximize the benefits of highly effective drugs and the obligation of fairness (ie, ensuring equitable access across patients and patient groups). Although these values may sometimes be in tension, incorporating multiple values into principles of allocation is widely accepted.<sup>21</sup> These basic principles led the WG to offer 6 specific recommendations (Table 1).

### 1. Support Current Measures (and Develop Innovative New Ones) to Prevent Future Drug Shortages at the National Level

#### *Ethical Rationale*

Although there is disagreement about what justice in health care requires, any plausible account must include reasonable access to drug treatments for potentially curable life-threatening diseases. This ethical mandate requires that laws, regulations, reimbursement schemes, and policy instruments minimize the economic, political, and manufacturing barriers that contribute to drug shortages. Patients, providers, pharmacists, health system leaders, payers, and policymakers have an obligation to engage in policy activities to prevent shortages of drugs that are critical to the effective management of serious illness.

#### *Background*

Although national policy was not the main focus of the WG, members recognized

**TABLE 1** Recommendations of the WG

	Recommendation
1	Support current measures (and develop innovative new ones) to prevent future drug shortages at the national level
2	Optimize and efficiently use supplies to reduce the likelihood and mitigate the effects of future shortages
3	Develop explicit policies that give equal priority during a drug shortage to evidence-based use of chemotherapy agents whether patients are receiving treatment within or outside a clinical trial
4	Create an improved, centralized clearinghouse for sharing information about drug availability and shortages
5	Explore voluntary sharing of drugs at the state, regional, and national levels
6	Develop a strategy for ongoing stakeholder engagement regarding managing drug shortages, with specific emphasis on patients and patient advocacy groups

how efforts since 2011 have prevented some drug shortages. In 2011, Executive Order 13588 directed the Food and Drug Administration (FDA) to deploy its full complement of legal and administrative tools to prevent shortages.<sup>22</sup> This directive included requiring drug manufacturers to report planned discontinuation of production, expediting review of new drug suppliers and manufacturers, and working with the Department of Justice to report hoarding or exorbitant pricing. The FDA Safety and Innovation Act of 2012 (FDASIA) extended reporting requirements to all manufacturers of FDA-approved products (including biological agents, if the FDA so interprets the regulations). The FDA can also publicly issue noncompliance letters to manufacturers who fail to report. Additionally, FDASIA requires that the FDA submit an annual drug shortage and amelioration efforts report to Congress. FDASIA required the FDA to establish a task force to develop and implement a strategic plan, released in October 2013, for enhancing responses to drug shortages.<sup>23</sup>

### Action Items

The WG supports the full implementation of existing legislative efforts, regulatory capabilities, and systematic studies of drug shortages as described in FDASIA. However, the approach to shortages remains primarily reactive by relying upon reporting of shortages as they occur. We therefore recommend the following additional actions by the relevant legislative and regulatory bodies

to help prevent drug shortages in pediatric oncology:

1. create a critical drug and critical drug shortage list for pediatric oncology, in coordination with pediatric oncologists, pharmacists, and industry (congruent with a proposed, although not enacted, 2012 Drug Shortage Prevention Act<sup>24</sup>);
2. implement a proposed FDA quality metric to incentivize and reward high-quality manufacturing practices<sup>25</sup>;
3. explore the likelihood that production will be stimulated by amending the Medicare Prescription Drug Improvement and Modernization Act of 2003 to allow greater price increases for generic oncology drugs on the critical drug list;
4. examine the feasibility of a national stockpile of critical drugs, analogous to the Centers for Disease Control and Prevention's Strategic National Stockpile, as previously considered by the National Cancer Institute<sup>26</sup>; and
5. explore international agreements to allow rapid access to international suppliers of ingredients or drugs during a shortage, with attention to expeditiously registering these drugs domestically to facilitate their reimbursement.

### Barriers

The WG recognized the government's inability to require manufacturers to

produce specific products in a market economy. Notwithstanding this hurdle, the following additional barriers must be addressed to achieve these action items:

- potential disagreement about which drugs are “critical” for specific diseases;
- the unproven effectiveness of new incentives, such as manufacturing quality metrics, which will require evaluation before full implementation;
- concerns about increased cost and reduced access, if generic drug prices increase;
- recognition that modification of existing legislation requires political will and significant time before implementation;
- the need to ensure, in coordination with international regulatory agencies, the quality of drugs (or ingredients) obtained internationally;
- the need to avoid exporting shortages due to increased US demand; and
- the need to address drug shortages across the spectrum of health care needs beyond pediatric oncology.

## 2. Optimize and Efficiently Use Supplies to Reduce the Likelihood and Mitigate the Effects of Future Shortages

### Ethical Rationale

During routine operations, high-value health systems should base clinical decisions on rigorous evidence and optimal resource utilization to deliver high-quality, efficient care.<sup>27</sup> These values are even more important during a drug shortage.

### Background

The WG discussed several examples where institutions and health systems optimized their local supplies to mitigate the effects of ongoing shortages.

For example, during the 1997–1998 intravenous immunoglobulin shortage, intensive and timely efforts were made to review the clinical evidence base supporting intravenous immunoglobulin use.<sup>28</sup> Elimination of uses lacking substantial evidence effectively mitigated the shortage. More recently, the Centers for Disease Control and Prevention and the Centers for Medicare and Medicaid Services clarified the permissibility of repackaging unopened vials for multiple patients within a hospital to reduce wastage.<sup>29</sup> WG members also described information technology innovations that use standard computer software to optimize drug supply use. For example, with appropriate safeguards, scheduling patients to receive infusions of scarce injectable drugs on the same day can reduce wastage. Finally, the WG discussed how some institutions, in an effort to increase effective supplies, have turned to “gray” (sometimes called “parallel”) market suppliers: wholesalers that operate outside normal distribution channels and stockpile drugs for later resale, often at exorbitant prices.<sup>11,30,31</sup>

### Action Items

The WG recommends that institutions and health systems, individually and collectively, do the following:

1. review proactively, in a standardized manner, the evidence-based indications for drugs at risk for shortage, which is a task best achieved through multiinstitutional collaboration and the involvement of relevant professional societies;
2. support collection of data necessary for creating and maintaining this evidence base, both to facilitate prioritization of uses of drugs in shortage and to support identification of safe and effective substitutions (eg, those recommended by COG), as part of a learning health system;
3. develop and disseminate strategies, including novel applications of existing software programs, to optimize use of supplies; and
4. create policies to identify, report, and avoid gray market suppliers, due both to concerns over their potential to exacerbate shortages and to questions about supply chain documentation.

### Barriers

Optimizing supplies poses challenges, including the following:

- inadequate evidence for many treatments in medicine, particularly in pediatric oncology, where off-label drug use is common;
- the political and public context of treatments, especially for rare or life-threatening diseases or diseases for which few alternatives exist, as a result of which prioritization efforts are likely to be controversial;
- disagreement about how to prioritize needs between divisions and departments, and between pediatric and adult patients, particularly when comparing evidence bases is difficult;
- the strong desire of clinicians, pharmacists, and institutions (motivated by concern for patient well-being) to use gray market suppliers in the short-term, notwithstanding these drugs' questionable pedigrees and the gray market's contribution to, or exacerbation of, shortages; and
- the absence of regulatory barriers to (1) prevent use of gray market suppliers (eg, laws or regulations that deny reimbursement or penalize institutional use of such supplies, although some proposals exist<sup>32</sup>) or (2) minimize the gray market's impact (eg, laws or regulations that prohibit reselling

drugs above a specified mark-up threshold).

### 3. Develop Explicit Policies That Give Equal Priority During a Drug Shortage to Evidence-Based Use of Chemotherapy Agents Whether Patients Are Receiving Treatment Within or Outside a Clinical Trial

#### Ethical Rationale

Most families of children with cancer are approached about research participation. Fairness requires sharing the benefits and burdens of research equitably, and ensuring that the decision to participate in research is free from coercion or undue inducement. During a shortage, tension might exist between use of a chemotherapy agent within a trial (which has the potential to benefit future patients as well as the children in the trial) and its use to treat children outside a trial.

#### Background

Nearly two-thirds of all children with cancer enroll in clinical trials, often via consortia such as COG.<sup>16</sup> Childhood cancer research is rightly credited with tremendous gains in cancer survival over the past 50 years. Detailed prioritization discussions were not the principal focus of this statement; however, the unique collaborative context of pediatric oncology motivated the WG to address prioritization in this discrete area. We therefore considered whether institutions might justifiably prioritize clinical trial participants over nonparticipants during a drug shortage. The WG considered 2 situations: (1) the scarce drug is the investigational agent in a clinical trial and has not yet been shown to be effective (or more effective than the alternatives) for the indication under study and (2) the scarce drug is part of a well-established standard backbone within a clinical trial, such that patients would likely receive the drug

regardless of whether they were participating in the trial.

### Action Items

The WG recommends that research consortia such as COG work with member institutions to

1. prioritize accepted and evidence-based uses of drugs over experimental uses during a drug shortage<sup>18</sup>; and
2. develop and endorse policies giving equal priority to patients receiving standard, evidence-based treatment with a chemotherapy agent, regardless of whether the patient is being treated within or outside a clinical trial.

### Barriers

Not affording research participants priority during a shortage may be controversial. The most significant barrier to this recommendation, rooted in a sense of reciprocity for these children's contribution to the generation of new knowledge and to future patients, is the viewpoint of some that trial participants deserve priority access to drugs. Ultimately, however, the WG concluded that concerns over undue inducement, public perception, and the imperative to use drugs for indications for which evidence of benefit exists outweigh arguments for giving priority access to research participants.

## 4. Create an Improved, Centralized Clearinghouse for Sharing Information About Drug Availability and Shortages

### Ethical Rationale

The WG endorsed the value of fairness, understood as equitable access to drugs across as well as within institutions. During a shortage, if some health systems and institutions are less able than others to manage drug shortages, their patients could experience unfairly diminished access. In some cases,

these patients might be members of disadvantaged groups due to socioeconomic status, race/ethnicity, or immigration status. Fairness, therefore, requires developing strategies to facilitate cooperation across institutions.

### Background

WG participants described the importance of accurate information about drug shortages, including expected duration and severity, as a prerequisite for effective management. For example, the FDA and the American Society of Health-System Pharmacists (ASHP) both maintain Web sites related to current and past drug shortages.<sup>33,34</sup> These valuable resources have limitations, including inaccurate or unreliable information about expected duration, inconsistent reporting requirements, and differences in Web site content. Many limitations relate to inadequate information provided to the FDA or the ASHP. Pharmacists therefore spend significant resources locating information about drug availability and shortages, often via informal personal contacts and social networks. Despite COG's invaluable role in facilitating such networks, contacts are not uniform, and some hospitals or health systems are less able than others to identify and manage impending shortages.

### Action Items

Recognizing the ad hoc, inefficient nature of current strategies for sharing information related to drug shortages, the potential for inequitable information access by health systems and patients, and the limitations of current online resources, the WG recommends that institutions, health systems, and industry work with the FDA and ASHP to

1. develop an accurate, comprehensive, controlled-access clearinghouse that is centrally managed and made available to health institutions and systems for sharing drug shortage

information (including expected duration, available alternatives and sources, and contacts);

2. develop a coordinated and authoritative system to declare when a drug is in short supply, perhaps building on the critical drug shortage list (see recommendation 1);
3. design an active notification system, thereby preemptively informing pharmacists and providers about drug shortages and the location of existing supplies; and
4. coordinate sharing drug shortage information, where possible, with similar initiatives internationally.

### Barriers

A dedicated information clearinghouse will face several challenges. The WG specifically discussed the following:

- the proprietary nature of drug shortage information, because manufacturers seek to maintain competitive advantage by withholding information about manufacturing problems;
- the absence, aside from public non-compliance letters, of penalties for manufacturers that fail to provide accurate and timely information;
- critical implementation questions regarding the cost of such a clearinghouse, its relationship to existing databases at the FDA and ASHP, and what organization(s) might host, support, and/or manage it; and
- the risk that increased availability of information about actual or threatened shortages might facilitate hoarding by some stakeholders, including gray market suppliers.<sup>35</sup>

## 5. Explore Voluntary Sharing of Drugs at the State, Regional, and National Levels

### Ethical Rationale

Drug supplies may be unevenly distributed during a shortage, with some institutions having a relative surplus

whereas others experience scarcity. In the setting of maldistribution, sharing of drugs between institutions might maximize health outcomes for patients while minimizing inequities across patients and patient groups. Sharing thus upholds the principle of distributive justice.

### Background

Existing prioritization plans repeatedly call for coordination between institutions in the face of shortages. However, no systematic, detailed, or widely publicized plans exist for sharing drugs, and interinstitutional and interstate transfer remains logistically and legally problematic. Regional systems exist for sharing resources in other contexts, such as the United Network for Organ Sharing or the Regional State Health Emergency Management Coalitions, motivating the WG to consider drug sharing in oncology. The WG recognized that sharing should not require 1 institution to deplete its supply to the detriment of its own patients, which raises questions of how to define “detriment,” “duration of responsibility,” and whether the depletion applies only to existing patients or anticipated ones. Nevertheless, a drug-sharing plan might reduce the degree to which maldistribution of supply exacerbates a drug shortage.

### Action Items

Implementing a drug-sharing plan would be a lengthy process, but the WG agreed that it deserves urgent attention, particularly by pharmacists, state boards of pharmacy, institutions, and health systems. These and other stakeholders should

1. join with legal specialists to examine state drug pedigree laws and pharmacy board rules to identify ways to facilitate interinstitutional and interstate transfer of drugs, especially during shortages;

2. support ongoing federal efforts to establish a national “track and trace” authentication system that might support interstate transfer<sup>36</sup>;
3. thoroughly examine the ethical obligation of institutions to prioritize “their own” patients over those at other institutions, including the relevance of this obligation during drug shortages and its relationship to institutional economic pressures; and
4. consider under what circumstances, if any, to centralize drug supply at a single regional center to minimize wastage, recognizing that this step would require patients to travel to the designated institution to receive the drug and that the need to travel might disadvantage vulnerable populations.

### Barriers

Practical and ethical barriers make sharing drugs challenging. The WG discussed the following barriers:

- different thresholds among institutions for what counts as “adequate” reserve, and whether these thresholds must be standardized and publicized in the clearinghouse;
- whether or to what degree institutional and health system optimization and prioritization schemes must be standardized (eg, to avoid rewarding institutions that prioritize uses, such as those supported by lesser evidence, that are deemed less defensible by the community);
- the need to account for changing demand across institutions over time, due to variations in diagnosis, volume, and other aspects of patient need;
- the need for cooperation among institutions that ordinarily compete to attract patients, including questions about whether institutions’

sharing (or receiving) drugs might negatively affect patients’ confidence in these institutions;

- the need for cooperation among pediatric and adult specialties that use the same drugs (eg, medical and pediatric oncology, rheumatology);
- how to manage liability if shared products are later found to have quality problems; and
- whether sharing mechanisms must be mandated (ie, by federal or state agencies or by payers) to be successful.

### 6. Develop a Strategy for Ongoing Stakeholder Engagement Regarding Managing Drug Shortages, With Specific Emphasis on Patients and Patient Advocacy Groups

#### Ethical Rationale

There are multiple justifications for engaging stakeholders, including procedural (as part of a fair process to involve affected individuals and groups), substantive (because engagement can contribute tangibly to improved plans), and practical (as a means to improve commitment to and implementation of a plan). Fundamentally, the ethical value of respect is demonstrated by ensuring that stakeholders have the opportunity to be informed about the problem and are invited to contribute to the solution.

#### Background

The WG emphasized that engagement with a comprehensive set of stakeholders, including patients and patient advocacy groups, is critical to the above recommendations. For example, widespread awareness and support of ongoing legislative efforts is necessary for the success of recommendation 1. Stakeholder engagement, particularly with patients and patient advocacy groups, will be similarly crucial for navigating the difficult context of evidence review in recommendation 2.

Recommendation 3 requires communication between hospitals and the academic research enterprise, in situations where these operate more independently. Patient representatives will have a role in the information clearinghouse proposed in recommendation 4. Finally, sharing of drug between institutions in times of shortage (recommendation 5) will require recognition not only of institutional ethical obligations but also of stakeholder views on this issue. WG members viewed successful examples of engagement in other areas, such as pandemic influenza planning, research, and resource allocation, as foundations for engagement in drug shortage management plans.

### Action Items

The WG recommends that industry, institutions, organizations, health systems, and relevant government agencies commit to meaningful stakeholder engagement on management of drug shortages by

1. emphasizing transparency as a value in planning processes, including financial analyses;
2. developing concrete strategies to engage patients and advocacy groups during all phases of planning for current and future drug shortages;
3. including patients and patient advocacy groups in research to provide a patient-centered and evidence-based rationale for shortage management; and
4. creating mechanisms (including an appeals process) for managing disagreement and arriving at reasonable decisions given their likely controversial nature.

### Barriers

Barriers to stakeholder engagement include the following<sup>37</sup>:

- the unpredictability and time-sensitivity of drug shortages,

highlighting the need for comprehensive, future-oriented planning;

- defining “stakeholders” for the breadth of decision-making (eg, patients, community members, clinical research subjects, and the broader public, recognizing that these may overlap);
- reducing barriers, including cost, language, literacy, and transportation, that might prevent some individuals or groups from participating; and
- educating the public and other stakeholders about drug shortage mitigation strategies, which require planning and commitment in advance of an actual shortage.

### CONCLUSIONS

The WG developed consensus around 6 broad recommendations and multiple specific action items for preventing and managing drug shortages in pediatric oncology. These recommendations provide a comprehensive blueprint for action to ensure that children with cancer maintain access to critical drugs needed to treat their disease. On the basis of fundamental ethical values and informed by a multiinstitutional and interdisciplinary group, the recommendations emphasize that solving the drug shortage problem is an ethical obligation as well as a practical problem. Although focused on pediatric oncology, our recommendations have obvious applicability to pediatrics and medicine generally.

Adopting these recommendations will be ambitious. Piecemeal implementation might improve aspects of the drug shortage problem. Institutions and health systems, for example, might be wise to implement recommendation 2 from the standpoint of efficiency. They can develop institutional policies regarding evidence-based uses of drugs, avoidance of gray market sources, and

stakeholder engagement that could set an example for other institutions and thereby shift norms and behaviors in a positive direction.

However, our recommendations will be most effective when implemented as part of a cooperative and integrated framework. This task can be best accomplished by the coordinated efforts of involved stakeholders, led by an expert panel including clinicians, legal scholars, bioethicists, patient advocates, and government and industry representatives. For example, sharing drugs (recommendation 5) is only possible if information about drug shortages is widely available (recommendation 4). This information can only be freely shared if the gray market is prohibited or effectively regulated (recommendation 2). Determining when sharing should occur, or which information must be shared, could require formal declarations of “critical drugs” and “critical drug shortages” (recommendation 1). Finally, stakeholder engagement (recommendation 6) should properly occur in conjunction with all other recommendations.

This cooperative approach will require broad, multilevel stakeholder support, both within federal, state, and local government and among industry, institutions, and relevant professional societies and organizations. Increasing awareness of the drug shortage problem and of these recommendations, followed by their review and adoption by individuals, institutions, and organizations within and beyond our WG, are critical next steps for preventing and managing future drug shortages.

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