

**The Impact of Drug Shortages on Patients with Cardiovascular Disease:  
Causes, Consequences, and a Call to Action**

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**Abstract**

Shortages of cardiovascular drugs have become increasingly common, representing an ongoing public health crisis. Given few therapeutic alternatives to many of the drugs in short supply, these shortages also pose a major challenge for cardiovascular care professionals. Although changes in the regulatory environment have led to some improvements in recent years, problems involving manufacturing processes remain the most common underlying cause. Due to the complex nature of drug shortages, sustainable solutions to prevent and mitigate them will require collaboration between regulatory agencies, drug manufacturers, and other key stakeholder groups. In this report, we describe the scope of the cardiovascular drug shortage crisis in the United States, including its underlying causes and the efforts currently being made to address it. Further, we provide specific recommendations for how cardiovascular care professionals can be involved in efforts to limit the impact of drug shortages on patient care as well as policy changes aimed at preventing and mitigating them.

**Key words:** drug shortages, policy, advocacy, regulatory affairs

## **Introduction**

In early 2014, reports of critical shortages in the supply of intravenous (IV) nitroglycerin emerged in news media, alerting the public to an issue that could affect thousands of patients presenting to the emergency department with acute ischemic heart disease each year.<sup>1</sup> As with the case of IV nitroglycerin, drug shortages occur when a disruption in supply alters the way a drug must be prepared or dispensed, or when it requires the use of an alternative therapy. Both scenarios have been implicated in patient harm due to delays in care as well as directly causing medication errors and other adverse events.<sup>2</sup> Although drug shortages had previously garnered only sporadic attention in the media, they have become a familiar aspect of contemporary clinical practice. This is especially true in acute and critical care settings, where complex clinical decision-making has been further compounded by limited access to common standards of care. Viable alternatives may exist in some scenarios but they often yield less than optimal outcomes.

The number of active drug shortages in the United States (US) has increased by over 7-fold since 2007, and a growing number of these has affected patients with cardiovascular disease (CVD).<sup>2</sup> Efforts to address drug shortages have focused both on prevention and mitigation strategies but their effectiveness has been limited. Given that more patients and families are impacted by CVD than any other condition, ongoing shortages in this setting have major public health implications.<sup>3</sup> Thus, this writing group comprised of members from the American Heart Association / American Stroke Association (AHA/ASA) was convened to examine the issue further; in the following report, we describe the scope of the drug shortage crisis in the US, with an emphasis on its impact in patients with CVD, as well as the underlying causes of drug shortages, efforts currently being made to address them, and recommendations for future action.

## **Current State of Cardiovascular Drug Shortages**

The US Government Accountability Office (GAO) recently highlighted the threat posed by drug shortages with data from the University of Utah Drug Information Service (UUDIS).<sup>2</sup> Although the US Food and Drug Administration (FDA) also provides information on drug shortages that may significantly impact public health, the UUDIS defines shortages more broadly, including those that affect how a pharmacy must prepare or dispense a product or those that require the use of alternative agents that may affect patient care.<sup>4,5</sup> The UUDIS is the most comprehensive source for

information on US drug shortages and regularly prepares reports for state and federal agencies. As shown in Figure 1, a promising downward trend has been observed in the number of new drug shortages reported each year, although shortages of cardiovascular drugs has remained fairly constant. Of note, these data are only a snapshot and do not reflect the number of active drug shortages extending over several years. Because many remain unresolved, the number of existing drug shortages remains high, as shown in Figure 2.

After excluding electrolytes and intravenous fluids, data from UUDIS indicate that 1 of every 10 shortages from January 1, 2001 to September 30, 2014 involved drugs used in the management of CVD (Table 1; Figure 2; Appendix 1). Of the 181 shortages involving cardiovascular drugs, the majority (68%) represented therapies used in the routine management of CVD (e.g., vasodilators and other antihypertensives, antiarrhythmics, diuretics). Another 19% represented drugs related to coagulation, thrombosis, or blood formation (e.g., heparin, blood factor products), and 13% represented vasoactive drugs (e.g., dopamine, norepinephrine), which are often required in critically ill patients. The duration of reported drug shortages varied widely, ranging anywhere from 4 days to 30.5 months. The most commonly cited reasons for drug shortages were problems associated with manufacturing and unknown causes. Additional details can be found in Appendix 1.

### **Causes of Cardiovascular Drug Shortages**

The underlying causes of drug shortages were not well-elucidated until after an analysis by the US Food and Drug Administration (FDA) was published in 2011.<sup>6</sup> In this report, manufacturing and economic factors were cited as the principal drivers of drug shortages, although the two were not mutually exclusive and may have together influenced drug supply. Of the 127 drug shortages from 2010 to 2011 listed in the FDA report, the most common factors resulting in supply disruptions were problems at the manufacturing facility (43%), delays in manufacturing or shipping (15%), and shortages of the active pharmaceutical ingredient (10%).<sup>6</sup> Altogether, problems related to manufacturing accounted for almost two-thirds of reported drug shortages. Another 8% represented cases where the manufacturer made a business-related decision to discontinue production. Less common reasons included increased market demand, shortage of non-pharmaceutical ingredients, and improper product labeling (a combined total of 10%). In 9% of cases, an underlying cause could not be identified.

Because efforts to ensure the integrity of the manufacturing process often influence the consistency of drug supply, the role of the FDA in drug shortages has been controversial. For example, in 2007, a number of serious adverse events and deaths occurred as a result of heparin contamination, prompting federal officials to exert greater pressure on the FDA to increase its inspections of manufacturing facilities abroad.<sup>7</sup> However, as was the case with heparin, more frequent inspections often increase the likelihood of identifying manufacturing violations. If remediation for these violations requires an interruption in production, a drug shortage may occur. Supplies of products for which there are few manufacturers, which is often the case even for generic medications, are particularly sensitive to disruptions in production. As a consequence, commonly used therapies are often disproportionately impacted by drug shortages.<sup>2</sup> The FDA has thus been assigned the arduous task of balancing concerns about the quality and integrity of the manufacturing process against the impact on drug supply.<sup>8</sup>

The manufacturing process is also substantially influenced by economic factors. The market for generic drugs is highly price-sensitive and rarely impacted by differences in quality.<sup>8</sup> Many assume that FDA approval signifies a certain standard of quality, but in reality the quality of marketed products may be highly variable and the ability for purchasers to ascertain it is challenging if not altogether impossible.<sup>9</sup> Furthermore, inadequate funding has limited the ability of the FDA to regularly inspect the growing number of worldwide manufacturing facilities responsible for the US drug supply.<sup>7</sup> As a consequence, the perceived threat of enforcement is modest at best, providing manufactures little incentive to invest in strategies that improve quality, and increasing the likelihood of supply disruptions when remediation is required. Thus, the confluence of these factors limits the extent to which quality informs purchasing decisions and as it does in other industries.

Other microeconomic factors may also contribute to drug shortages, particularly for medically necessary drugs such as those used in the management of patients with CVD in acute and critical care settings.<sup>10</sup> The price-responsiveness of demand for many of these drugs is low in the short-term, meaning that increases in price do not substantially reduce demand. As a consequence, in contrast to other commercial markets where price can have a significant impact on consumer decision-making, health care facilities must purchase medically necessary drugs regardless of their price. This is further exacerbated by limited competition in the market, especially for drugs made by a single manufacturer. Additionally, the relative price-insensitivity of demand is further compounded by the fact that the

end-users of drugs often do not directly experience the effects of price increases. For example, health care facilities, which often receive capitated payments from health insurers for products and services rendered, may be unable to bill for the added cost of a medication if the price increases. When possible, health insurers may simply pass the added cost on to beneficiaries, but only after the product or service has already been consumed (e.g., the life-saving or other medically necessary drug has already been administered), thereby preventing it from influencing consumer decision-making. Finally, from a supply standpoint, increases in manufacturing capacity are not often economically feasible, especially in the short term, thus supply will not increase despite an increase in price.

Although other factors (e.g., changes in practice trends, natural disasters) may contribute to drug shortages, a substantial impact has not been observed in formal analyses.

### **Case Examples**

#### *Heparin*

Beginning in 2007, serious injuries and deaths were linked to contaminated heparin products manufactured in China, which led to a massive recall by Baxter Healthcare in February of that year.<sup>11</sup> From January 1, 2007 to May 31, 2008, 149 deaths in 11 countries (81 in the US) were associated with the administration of heparin to patients who subsequently developed hypersensitivity and/or hypotension. Researchers at the FDA attributed these reactions to over-sulfated chondroitin sulfate (OSCS), a contaminant that mimics the activity of heparin so closely that it could not be identified by contemporary standards. A plausible physiologic mechanism for the reactions was confirmed when analyses by the FDA demonstrated that OSCS directly activates the kinin-kallikrein pathway, leading to the generation of bradykinin, a potent vasoactive mediator, and C3a and C5a, two potent anaphylatoxins.<sup>11,12</sup>

For decades, American manufacturers outsourced intestinal hog mucosa, the main source of the raw ingredients used in heparin, due to insufficient domestic supply.<sup>13,14</sup> Approximately 75% of the crude porcine heparin used to manufacture heparin is derived from outside the US; China serves as the main source, providing over 60%.<sup>14</sup> During a February 2008 visit to the Chinese manufacturer responsible for heparin production, the FDA discovered multiple deficiencies in quality control and other manufacturing processes.<sup>12</sup> Following a detailed investigation, the FDA concluded that the heparin had also been intentionally adulterated with OSCS to reduce production costs, resulting

in products that were 100 times less expensive than standard heparin.<sup>15-17</sup> Additionally, many of the farms, slaughterhouses, and other suppliers of raw heparin were being poorly regulated, contrastingly sharply to the strict manufacturing processes in the US and Europe.<sup>15,16</sup>

As illustrated in this case, over-reliance on a predominant source of active ingredient posed a major threat to the drug supply chain. Until Chinese sources of heparin can be monitored more stringently, the potential for adulteration and other violations of current good manufacturing practices (CGMP) remain a threat. Although several alternatives to heparin exist, they are often more costly, have fewer indications, and lack the vast production capacity of heparin.<sup>14</sup> Ongoing concerns about the potential for heparin shortages has prompted the FDA to consider reintroducing bovine heparin to the US market, which was voluntarily removed in the 1990s due to concerns over bovine spongiform encephalopathy (BSE).<sup>14</sup> However, recent FDA analyses indicate that existing manufacturing processes can remove or inactivate BSE agents. A more diversified supply chain would provide more stability in the heparin market and likely prevent shortages of such a widely used and critically necessary drug product.<sup>14</sup>

### *Nitroglycerin*

The role of IV nitroglycerin as a drug of choice in several cardiovascular disorders has forced clinicians to ration supply in the face of critical drug shortages. Although shortages of IV nitroglycerin emerged as early as 2007, their impact on patient care began to garner national attention in the spring of 2014.<sup>1</sup>

Causes of the current IV nitroglycerin shortage are multifactorial. In January 2014, Baxter Healthcare began rationing its supply after failing to meet the increased demand that resulted when Hospira and American Regent discontinued their products in Fall 2013.<sup>1,18,19</sup> Hospira discontinued their premixed product due to unspecified manufacturing delays, whereas manufacturing upgrades required of American Regent as part of remediation processes resulted in discontinuation of its vials for reconstitution.<sup>18</sup> In March 2014, Baxter Healthcare halted nationwide distribution due to a manufacturing defect in rubber stoppers. As recently as December 2014, Baxter Healthcare continued to announce shortages of premixed IV nitroglycerin, which it now attributes to a shortage of raw material. Neither Hospira nor American Regent has issued release dates regarding their respective products, extending the current IV nitroglycerin shortage to over a year in duration.<sup>18</sup> As part of an agreement with the FDA,

Arbor Pharmaceuticals began importing a formulation of nitroglycerin marketed as glyceryl trinitrate (Nitronal®).<sup>18</sup> Although glyceryl trinitrate is manufactured by Pohl-Boskamp at its FDA-approved facility in Germany, introduction to the US market may introduce dosing errors due to the use of a different concentration compared to the US product.

As with heparin, the shortage of IV nitroglycerin illustrates the fragile nature of the drug supply chain. Although a small number of competing manufacturers exist in the case of IV nitroglycerin, it is subject to many of the same issues implicated in the heparin shortage. Imported products can be helpful in alleviating drug shortages but they can also increase the risk of medication errors in pharmacy automation systems due to differences in packaging or lack of bar codes or National Drug Code (NDC) numbers. Notably, imported products must be accompanied by a “Dear Healthcare Provider” letter outlining differences from the domestic product (e.g., dosing, concentrations). However, as with other instances when an alternative product must be used (i.e., even for those products manufactured in the US), differences in concentration and other product attributes have resulted in medication errors implicated in patient harm.<sup>20-23</sup> As was true with the heparin shortage, diversification of the drug supply chain would help create a more reliable and stable system, thereby preventing critical drug shortages before they impact patient care.<sup>24</sup>

### **Impact of Cardiovascular Drug Shortages on Patients, Providers, and Health Systems**

The absence of a mandatory national reporting system for adverse drug events has made it difficult to quantify the effect of drug shortages on patients with CVD. Most of the data on their impact has been generated from surveys conducted by the Institute for Safe Medication Practices (ISMP). In an ISMP survey from 2010, one in five clinicians reported that patient harm had occurred as a result of a drug shortage.<sup>22</sup> Specific examples included adverse drug events attributed to incorrectly compounded heparin during a shortage of premixed bags and two deaths attributed to a shortage of epinephrine.<sup>22</sup> Many clinicians also indicated that patient harm attributed to drug shortages was underreported. As a consequence, directly associating drug shortages with threats to patient safety has remained a challenge, which has likely slowed prevention and mitigation efforts.

As detailed in a recent review, drug shortages have been especially challenging in the setting of CVD because many of them represent first-line therapies where few evidence-based alternatives exist.<sup>25</sup> According to the 2010 ISMP

survey, 80% of clinicians reported difficulty in obtaining suitable alternatives to drugs in short supply, and 70% reported that no suitable alternative was available.<sup>22</sup> Medically necessary therapies, such as antiarrhythmics, antihypertensives, blood factor products, inotropes, vasopressors, and diuretics have recently been in short supply, often simultaneously (Table 1). A dearth of evidence-based alternatives has therefore required the use of second- or third-line therapies that are often less effective or confer a greater risk of adverse effects.<sup>22</sup> In some cases, shortages have required that clinicians ration therapy, resulting in ethical dilemmas that only further confound patient care.<sup>26</sup>

Medication errors associated with drug shortages represent a similar threat to patient safety. Errors are more likely to occur when a different product (i.e., strength, formulation) must be substituted for a drug in short supply or when clinicians are unfamiliar with an alternative agent. According to ISMP, one-third of clinicians reported a near miss at their institution as a result of drug shortages, and one-fourth reported that errors had actually occurred.<sup>22</sup> As with adverse events, error reporting is also voluntary, meaning that these estimates likely underrepresent the true number of errors that have occurred.

The economic implications of drug shortages have also been difficult to estimate. Alternatives to drugs in short supply may be more costly, but estimates of the financial impact of drug shortages should also account for their impact on non-drug expenses, such as the cost of any interventions required to prevent or alleviate harm as a result of shortage-related medication errors, or increased lengths of stay as a result of less efficacious alternatives. Additionally, estimates should consider the added cost of labor required to manage shortages and their impact on patient care. Based on a survey of pharmacy directors in 2010, the estimated annual labor costs associated with managing drug shortages was \$216 million; at that time, the number of active drug shortages was approximately half what it is now (152-188 in 2010 versus over 300 in 2014) (Figure 2).<sup>27</sup>

Another unfortunate consequence of drug shortages is tension among health professionals. Often these frustrations originate from a lack of understanding about the underlying causes of drugs shortages as well as the limited influence that individual institutions may have on them. Nonetheless, these frustrations can result in misplaced blame and impair the interdisciplinary collaboration required to successfully manage drug shortages at the institutional level. For example, prescribers aggravated by an inadequate supply of critically necessary therapies

may vent their frustrations to pharmacy or nursing staff; in fact, over half of respondents to the 2010 ISMP survey reported anger among physicians over issues related to drug shortages.<sup>22</sup> Similarly, pharmacy staff may place blame on prescribing practices or non-adherence to efforts being implemented to manage drug shortages. Nursing staff may also receive criticism for wasting drugs in short supply.

Finally, confidence in the quality of drug products has waned as a consequence of limited transparency in manufacturing and distribution processes as well as increasingly widespread reports of regulatory violations, such as the FDA inspection of the Indian pharmaceutical manufacturer Wockhardt, Ltd. that revealed egregious violations of CGMP.<sup>28</sup> Although the FDA releases information about violations uncovered during its inspections, the specific products made at these facilities are not disclosed. Additionally, FDA regulations do not require suppliers to disclose which firm originally manufactured a product or where production occurred, thus preventing purchasers who wish to avoid certain manufacturers from being able to do so.<sup>29,30</sup> The origin of an FDA approved product is further obfuscated by the practice of contract manufacturing, where drug products are made for other suppliers to sell under a different label. For example, Isuprel<sup>®</sup> (isoproterenol) is marketed by Valeant Pharmaceuticals but manufactured by Hospira; however, the role of Hospira as the actual manufacturer of Isuprel<sup>®</sup> is not included in product labeling. As a consequence, purchasers are often unable to ascribe responsibility for the quality of a specific drug product to its respective manufacturer. Additionally, purchasers may pay high prices to firms that did not invest in the development or manufacturing of the original product.

A related threat to the quality of the drug supply has been the use of unauthorized distributors, also known as the “gray market.”<sup>31</sup> In response to growing anxieties among purchasers who have been unable to secure medically necessary drugs, gray market distributors have exploited the drug shortage crisis by offering drugs in short supply, often at exorbitant prices. Because gray market distributors operate outside traditional supply chains, purchasers may be unable to verify the pedigree of a drug product or determine whether quality has been compromised due to poor storage conditions or by introduction of recalled or counterfeit products.

### **Current Efforts to Prevent and Mitigate Cardiovascular Drug Shortages**

Over the last five years, several government agencies and stakeholder organizations have launched initiatives to address drug shortages (Figure 3). In November 2010, a Drug Shortages Summit was convened by the American Society of Health-System Pharmacists (ASHP), the American Society of Clinical Oncology (ASCO), ISMP, and the American Society of Anesthesiology.<sup>32</sup> Recommendations from the summit included a call for changes in the regulatory oversight of the FDA and improved communication among the agency, drug manufacturers, and other stakeholders. In response, the FDA conducted a public workshop in September 2011 and a Presidential Executive Order was issued the following month.<sup>33,34</sup> Altogether, these combined efforts resulted in the passage of the FDA Safety and Innovation Act (FDASIA) in July 2012, which expanded the regulatory authority granted to the FDA and required manufacturers to notify the agency at least 6 months in advance (or as soon as practicable) of any interruptions or discontinuations in the production of life-saving drugs or those used for debilitating diseases.<sup>35</sup> Additionally, FDASIA mandated that the FDA develop a strategic plan for addressing drug shortages and provide Congress with annual reports; an inaugural report was submitted in October 2013.<sup>36</sup>

Since the enactment of FDASIA, notifications from manufacturers to the FDA have increased six-fold, allowing the agency to prevent or mitigate a greater number of new shortages.<sup>2</sup> Steps taken by the FDA have included working with alternative manufacturers to offset interruptions or discontinuations, using regulatory discretion to allow products with minor defects to remain available (provided the defects do not place patients at risk and health professionals are notified), introducing alternative products to the market (e.g., temporary importation from other countries), and expediting reviews of new suppliers and drug applications (Table 2).<sup>2</sup> However, the effectiveness of these strategies depends largely on the promptness and transparency of communication between the FDA and key stakeholders. To that end, the FDA and ASHP have committed to regularly publishing drug shortage information.

As required by FDASIA, the FDA issued a strategic plan for preventing and mitigating drug shortages in October 2013.<sup>37</sup> Its first goal was to strengthen the agency's mitigation response once notified of a supply disruption or shortage; tasks necessary for fulfilling this goal included streamlining the efficiency of its response, improving data and response tracking, clarifying the roles and responsibilities of manufacturers, and enhancing public communication regarding drug shortages. The agency's second goal was to develop long-term strategies to address the underlying causes of supply disruptions in order to prevent future drug shortages; tasks related to this goal

included developing methods to incentivize and prioritize manufacturing quality, using regulatory science to identify the early warning signs of shortages, and increasing knowledge about issues related to drug shortages among stakeholders in order to develop new prevention and mitigation strategies.

Although efforts to date have likely reduced the emergence of new drug shortages, the number of existing shortages remains high, indicating that opportunities for improvement exist.<sup>2,38</sup> As a follow-up to its initial findings in 2011, the GAO issued another report in February 2014 indicating that drug shortages remained a threat despite the FDA's efforts.<sup>2</sup> Although the GAO acknowledged that the FDA had made significant progress since 2011, it also highlighted persistent shortcomings, including several deficiencies in the quality and reliability of the agency's drug shortages database, which could be useful for identifying early warning signs for shortages as well as evaluating the impact of prevention or mitigation strategies. Also included in the GAO recommendations were that the FDA perform periodic analyses to systematically assess information and proactively address drug shortages.

The FDA's short-term efforts have made it more effective at mitigating new drug shortages and its long-term plans should further improve the situation, but a comprehensive solution cannot be implemented by the FDA alone. In fact, the FDA may already be at maximum capacity given current limitations in its resources and regulatory authority.<sup>7</sup> Furthermore, many of the root causes of drug shortages are outside the purview of the FDA or are a result of manufacturing issues upon which the agency has only minimal influence. For example, the FDA cannot require that a company manufacture a product nor can it manufacture products on its own. Additionally, expecting that the FDA be responsible for inspecting the entire supply chain of every manufacturer is not feasible given that an estimated 80% of the active pharmaceutical ingredients in US drugs are manufactured abroad and the resources allocated to the FDA for inspections remain limited.<sup>39</sup> Finally, preventive strategies depend heavily on timely notification from manufacturers as well as their cooperation in efforts to prevent or mitigate them. Thus a more comprehensive solution involves manufacturers taking greater responsibility for the quality of their products as well as the integrity of the supply chain.

In 2013, the International Society for Pharmaceutical Engineering (ISPE), an organization representing members from across the pharmaceutical manufacturing industry, issued a multidimensional prevention plan for drug

shortages focusing on corporate quality culture, quality-control systems, development and use of adequate performance and quality metrics, design and implementation of business continuity plans, communication with authorities, and building capabilities of the organization and personnel.<sup>40</sup> The plan itself represents an important step for the industry, as it recognizes the complexity of the problem as well as the central responsibility manufacturers have for exploring and implementing solutions. It also assigns global health authorities and other regulatory agencies like the FDA the role of facilitating a comprehensive response involving multiple manufacturers.

Recognizing that a collaborative approach is necessary for discovering sustainable solutions to the drug shortage problem, several stakeholder groups have also issued guidance documents to assist in prevention and mitigation strategies. Additionally, several groups were instrumental in facilitating conversations surrounding the issue as well as for advocating for legislative and regulatory changes that made it possible for many of the current strategies to be implemented. These organizations have included the American Medical Association, American College of Cardiology, American Hospital Association, ASCO, and ASHP.

### **Call to Action: Recommendations for Cardiovascular Care Professionals and Policymakers**

Given the detrimental impact of drug shortages on patients with CVD, the writing group makes the following recommendations (summarized in Table 3):

#### Recommendations for Cardiovascular Care Professionals

*Form diverse, multidisciplinary task forces to prevent and mitigate drug shortages.*

Every institution involved in the care of patients with CVD should form a task force charged with addressing drug shortages. For institutions that exist as part of a larger network, a task force at the system level may be more appropriate. Given the number of patients with CVD affected by drug shortages, inclusion of a cardiovascular care professional should be strongly considered. Consideration should also be given to the formation of regional task forces to coordinate efforts among individual institutions and health systems. Drug shortages uniquely impact the critical interface between health care operations and clinical care, thus task forces should include representatives from both groups. At an institutional level, the task force should report to the Pharmacy and Therapeutics

Committee, as decisions regarding drug shortages often impact formulary decision-making. In addition to strategies for preventing and mitigating drug shortages, the task force should also be charged with many of the other recommendations included below, such as advocating regulatory changes and developing a clear and consistent communication strategy. In fulfilling each of the aforementioned roles, members should ensure the task force adheres to relevant federal and/or state regulations to avoid any inadvertent violations of antitrust law.

Given implications for the economic viability of health care facilities, efforts to address drug shortages should be coordinated between an institution's finance office and pharmacy administration. The unexpected nature of most drug shortages may require that institutions provide pharmacy administrators with flexibility in their operating budget as well as opportunities to adjust in response to drug shortages. Correspondingly, pharmacy administrative staff should develop processes for continuously monitoring drug inventory and anticipating new or worsening shortages. When drug shortages do occur, they should be validated with the manufacturer and communicated to the FDA and other regulatory bodies. Administrative and operational staff should also collaborate with clinicians to implement strategies aimed at reducing waste, such as streamlining drug preparation and distribution.

Because drug shortages impact every stage of the medication use process, all members of the cardiovascular care team, including physicians, pharmacists, advanced care providers, and nurses should be involved in efforts to address them. Strategies include the development of clinical guidelines for therapeutic alternatives and prioritization of patients who should receive drugs in short supply. Team members should also identify strategies unique to their practice. For example, nurse leadership may consider implementing a double-check for drugs in short supply (i.e., confirming with a provider prior to spiking a new bag). Similarly, team members should identify best practices for communicating new or updated shortage information to their individual departments.

Although drug shortages have disproportionately affected acute and critical care settings, an impact on medication therapies used for chronic management of CVD in ambulatory care settings (e.g., carvedilol, digoxin, isosorbide dinitrate) has also been observed. As in health care facilities, a multidisciplinary effort should be implemented to safely transition patients to alternative therapies when shortages occur. Community pharmacists can be especially helpful in this process by communicating promptly with local cardiovascular care professionals when shortage

information is provided by pharmacy distributors. Most pharmacists are capable of generating reports detailing dispensed medications (including associated prescribers), allowing them to identify patients who may be affected by an impending shortage as well as which professionals should be contacted. Similarly, community pharmacists are ideally positioned to work with providers on identifying viable alternatives based on current inventory or options provided by distributors.

*Develop and implement strategies to prevent and mitigate drug shortages that integrate clinical, economic, and regulatory considerations.*

Similar to the guidance promulgated by the American Heart Association and American Stroke Association (AHA/ASA) on drug formularies,<sup>41</sup> the writing group advocates that strategies for addressing drug shortages take into account clinical, economic, and regulatory considerations.

Patient safety should be the primary concern, and selection of therapeutic alternatives for drugs in short supply should be based on the best available evidence. Guidelines should be developed to assist clinicians in the appropriate use of therapeutic alternatives, including patient-specific considerations (e.g., age, gender, comorbid conditions, metabolic function, and pregnancy status) that might preclude their use. Additionally, guidelines should provide avenues for which restrictions on shorted drugs can be overridden when alternatives may not be in the best interest of the patient. Members of the cardiovascular care team should proactively and collaboratively develop these guidance documents for their institutions given unique expertise in the management of CVD.

Although economic considerations should be taken into account when developing strategies to address drug shortages, precedence should remain on safety and efficacy when possible. Additional consideration may be necessary when economic constraints inadvertently place other populations at risk (e.g., changes in practice trends that might lead to a drug shortage affecting other patients). Cardiovascular care professionals may be especially helpful in this regard, as they can represent the unique needs of the CVD population. Finally, efforts by organizations to take unfair advantage of the marketplace (e.g., stockpiling by health systems with greater purchasing power) should be discouraged, as this ultimately exacerbates drug shortages and places patients at risk.

Inherent in balancing safety and efficacy with cost is ensuring the quality of drug product. To maintain adequate drug supply at a reasonable cost, institutions may consider obtaining products through alternative means. However, use of unauthorized “gray market” distributors should be avoided. Other quality-based purchasing strategies include verifying the pedigree of drugs obtained through alternative wholesalers and avoiding manufacturers with egregious regulatory violations or a consistent disregard for CGMP.

*Educate key stakeholders (e.g., clinical and operational staff, administrators) on the underlying causes and consequences of drug shortages as well as efforts to address them.*

Misinformation about the underlying causes of drug shortages may escalate tensions among health care professionals, which may ultimately impair prevention and mitigation strategies. A goal of this document is to raise awareness of the issue, but educational efforts should also be implemented at the institutional level, where the specific needs of the organization can be met. This is especially true at large medical centers due to the turnover of professional training programs (e.g., residencies). Strategies to raise awareness at the institutional level may be further complemented by continuing education programs offered by professional organizations. Cardiovascular care professionals should seek opportunities to provide education on drug shortages impacting patients with CVD.

Educating key stakeholders on drug shortages should focus on identifying solutions proactively. Educational outreach should especially be provided to health professionals and administrators in order to facilitate their collaboration in strategies aimed at addressing drug shortages. Ideally, the content of education should include the causes and consequences of drug shortages, efforts being made to address them (particularly at the institutional level), how individual providers can uniquely assist the institution in their areas of practice, and where shortage resources (e.g., clinical guidelines) are located. Patient education should also be considered, as it may allay fears when standards of care are unavailable, particularly for patients who have been stabilized on a chronic medication and must be changed to an alternative as a result of a new drug shortage.

Although the frequency of educational efforts should be tailored to the individual needs of the institution, annual or semiannual education should be considered. Requiring that new employees complete a competency on drug

shortages during the orientation process may also prevent misinformation. Periodic updates on drug shortage information should be provided, with references to more comprehensive information as an additional resource.

*Serve as content experts on drug shortages when they are highlighted in the media.*

Representatives of the media may not understand the scope and complexity of the drug shortage issue. Misinformed reporting may only sensationalize the issue, impairing efforts to prevent or mitigate shortages. Cardiovascular care professionals should seek opportunities to serve as content experts on drug shortages. Proactively speaking on the issues ensures that experts remain at the forefront of the story, which may more effectively mobilize public support and advocacy efforts. To effectively reach the public, experts should embrace both traditional (e.g., print, television, radio) and emerging platforms (e.g., web, social media).

Voluntary health organizations, patient advocacy organizations, and specialty societies should also offer their members as experts on drug shortages. Providing expert testimony on health policy issues and responding to media requests are central to the work of the AHA/ASA Office of Public Advocacy and similar groups within other voluntary health or patient advocacy organizations. In addition, these organizations alert agencies and media outlets to experts in their community who can help them address specific issues raised by their work. With regard to drug shortages, these experts should be used as a resource to help the public understand the underlying causes, potential solutions, and current actions being undertaken to address them.

### Recommendations for Policymakers

Recommendations to strengthen the key legal and regulatory efforts already underway include the following:

#### *Develop a clearinghouse for drug shortage information*

As some organizations have already suggested, the FDA should collaborate with key stakeholders to develop a controlled-access clearinghouse for drug shortage information (e.g., current and past shortages, expected duration of each shortage, contacts).<sup>42</sup> Although the FDA and ASHP have developed web sites that collate this type of data, the focus of each is different and the two lists are rarely consistent. Additionally, because information publicly reported by the FDA is often limited to drug shortages with significant public health implications, it does little to reduce the

risk posed to patients when alternative products must be used to address relative drug shortages, such as medication errors resulting from products manufactured as a different concentration than the standard product.

Ideally, this drug shortage clearinghouse would interface with an active notification system alerting institutions and key stakeholder organizations to new shortages as well as updated information on existing shortages. Although a mobile app recently launched by the FDA is a promising first step, the information publicly reported by the agency often represents those shortages that have already become public health crises, which only delays clinician response while simultaneously heightening public concern.<sup>43</sup> With access to an updated information clearinghouse coordinated by the FDA, stakeholder organizations would have an opportunity to provide recommendations on prevention and/or management strategies before drug shortages become public health crises. Although comprehensive guidelines may be helpful for general management strategies or for prolonged drug shortages, practice alerts would likely be the most effective approach to disseminating information related to shortage prevention and mitigation strategies. In addition to advocating for these regulatory initiatives, cardiovascular care professionals can be further involved by developing recommendations to be included in practice alerts involving shortages that impact patients with CVD.

#### *Implement metrics to incentivize and reward manufacturer reliability*

The FDA should implement a metric to incentivize and reward the reliability of manufacturers as part of existing CGMP. Although the FDA recently created an award program to publicly recognize manufacturers who have supported the agency's efforts to address drug shortages, this is unlikely to have the same impact as financial incentives or penalties.<sup>44</sup> As some organizations have suggested, a "failure to supply" metric, which would designate those manufacturers who have been consistently unable to meet product demand, might assist institutions in drug purchasing and planning.<sup>45</sup> Exceptions would be needed so that manufacturers are not unfairly penalized for situations out of their control, such as the departure of other manufacturers from the market or a shortage of active pharmaceutical ingredients. This "failure to supply" measure, if properly constructed, would provide manufacturers with a powerful financial incentive to enhance the reliability of their supply.

#### *Require greater transparency in product labeling*

Greater transparency in the manufacturing and distribution process is needed to better assist institutions in making quality-based purchasing decisions. Currently, suppliers may choose whether to list a drug manufacturer, packer, or distributor in the labeling for a specific product but not necessarily the original manufacturer. To assist purchasers in making decisions about the quality of drug products, the FDA should require that the package labeling for a specific drug product disclose the original manufacturer. Additionally, the FDA should disclose the specific drug products made at facilities where violations of CGMP regulations have occurred.

#### *Increase funding for efforts aimed at addressing drug shortages*

Although the FDA is implicated in many of the strategies recommended above, any changes to its regulatory authority should be met with an appropriate allocation of funding and other resources. To implement the expanded responsibilities mandated by FDASIA and other recent legislation, the FDA has requested a 9% increase in its budget (up to a total of \$4.9 billion) for fiscal year 2016.<sup>46</sup> Included in the agency's budget is a \$33.2 million request to improve its ability to regulate drugs and other medical products. Cardiovascular care professionals calling for additional regulatory oversight by the FDA should likewise advocate that federal legislators allocate the funding necessary to implement prevention and mitigation strategies.

#### **Conclusion**

As detailed in this review, cardiovascular drug shortages remain common and represent a significant threat to public health and a major challenge for cardiovascular care professionals. Although the causes of these shortages are often multifactorial, most involve manufacturing processes. Given few alternatives to many of the therapies used for CVD, shortages have impacted patients in a variety of ways. The dilemmas resulting from these shortages have also heightened frustrations among clinicians and added substantial burden to the health workforce. Although recent efforts by the FDA have reduced the number of new shortages, the prevalence of ongoing shortages remains high. As a consequence, sustainable solutions will also require cooperation among manufacturers and key stakeholder groups. Individuals involved in the care of patients with CVD can contribute at an institutional level by forming multidisciplinary task forces to address drug shortages, educating key stakeholders on the issues, advocating legislative and regulatory changes that address the underlying causes of drug shortages, and serving as content experts when issues related to drug shortages arise in the media.

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**Table 1. Select Cardiovascular Drug Shortages Reported Between January 1, 2001 and September 2014.**

<b>Drug Class</b>	<b>Agents</b>
<b>Anti-Anginals</b>	Isosorbide dinitrate, isosorbide mononitrate, nitroglycerin*
<b>Antiarrhythmics</b>	Amiodarone*, disopyramide, dofetilide*, lidocaine, mexiletine, procainamide*, sotalol*
<b>Anticoagulants</b>	Argatroban*, enoxaparin, heparin*, lepirudin*, warfarin*
<b>Antihypertensives</b>	Chlorthalidone, clevidipine, clonidine*, doxazosin*, enalaprilat, hydralazine, hydrochlorothiazide*, isradipine*, losartan*, nicardipine, nifedipine*, prazosin, reserpine, valsartan*
<b>Diuretics</b>	Bumetanide, chlorothiazide*, chlorthalidone, ethacrynic acid*, furosemide*, hydrochlorothiazide, torsemide
<b>Fibrinolytics</b>	Alteplase, streptokinase*, tenecteplase, urokinase
<b>Hemostatic Agents</b>	Aminocaproic acid*, anti-inhibitor coagulant complex <sup>†</sup> , aprotinin*, factor IX products <sup>‡*</sup> , factor VIII products <sup>§*</sup> , protamine*, thrombin
<b>Rate Control Agents</b>	Carvedilol*, digoxin*, diltiazem, esmolol, labetalol*, metoprolol, propranolol*, verapamil*
<b>Inotropes/Vasopressors</b>	Dobutamine, dopamine*, epinephrine*, norepinephrine, phenylephrine*
<b>Miscellaneous</b>	Clofazolin, ezetimibe/simvastatin, fenofibrate*, gemfibrozil, pentoxifylline, phentolamine*, ticlopidine

\*Shortage reported in multiple years between 2001 and 2014

<sup>†</sup>Includes AutoplexT<sup>®</sup>, Feiba VH Immuno<sup>®</sup>

<sup>‡</sup>Includes AlphaNine SD<sup>®</sup>, Profilnine SD<sup>®</sup>, Benefix<sup>®</sup>, Mononine<sup>®</sup>, Proplex<sup>®</sup>

<sup>§</sup>Includes Alphanate<sup>®</sup>, Helixate<sup>®</sup>, Humate-P<sup>®</sup>, Monoclate P<sup>®</sup>, Recombinate<sup>®</sup>, Hemofil M<sup>®</sup>, Kogenate FS<sup>®</sup>, Koate<sup>®</sup>, Refacto<sup>®</sup>, Hyate C<sup>®</sup>

**Table 2. Example Actions Taken by the FDA to Prevent and Mitigate New Drug Shortages**<sup>36,37</sup>

<b>Problem</b>	<b>Action</b>
Loss of supplier of an active pharmaceutical ingredient	Expedite review of a new supplier
Impending product interruption or permanent discontinuation by one manufacturer	Inform other manufacturers of potential or actual shortage and query support capabilities  Encourage alternative manufacturers to increase production of that product
Medically essential drug with known quality issues (e.g. labeling, particulate matter in a sterile injectable)	Use regulatory discretion to allow distribution of the drug product after determining that the benefits of product availability outweigh the potential risks
Impending shortage of a critical drug	Allow temporary importation of medically necessary drugs from outside the US when no US alternatives are available  Use regulatory discretion for a new supplier of medically necessary drugs

**Abbreviations:** FDA – United States Food and Drug Administration; US – United States

**Table 3. Addressing Drug Shortages: Recommendations for Cardiovascular Care Professionals and Policymakers**

Form diverse, multidisciplinary task forces to prevent and mitigate drug shortages.

- Integrate all members of the cardiovascular care team, including physicians, pharmacists, nurses, nurse practitioners, and physician assistants
- Facilitate collaboration between operations and clinical staff
- Develop processes for monitoring drug inventory and communicating shortage information
- Communicate to the FDA and other relevant regulatory bodies when shortages occur

Develop and implement strategies to prevent and mitigate drug shortages that integrate clinical, economic, and regulatory considerations.

- Consider economic constraints but prioritize patient safety
- Develop policies, protocols, and/or guidelines to guide clinicians on the use of alternatives
- Determine how restrictions can be overridden when not be in the best interest of the patient
- Discourage taking unfair advantage of the marketplace (e.g., stockpiling) or using unauthorized distributors (i.e., gray market)
- Use quality-based purchasing strategies (e.g., avoiding manufactures with regulatory violations)

Educate key stakeholders on the underlying causes and consequences of drug shortages as well as efforts to prevent and mitigate them.

- Raise awareness of the issue at the organizational level
- Place focus on proactively identifying solutions to drug shortage problems
- Include administrative, operational, and clinical staff
- Require new employees to undergo education during the orientation process
- Provide periodic updates on new, ongoing, and resolved drug shortages

Serve as content experts on drug shortages when they are highlighted in the media.

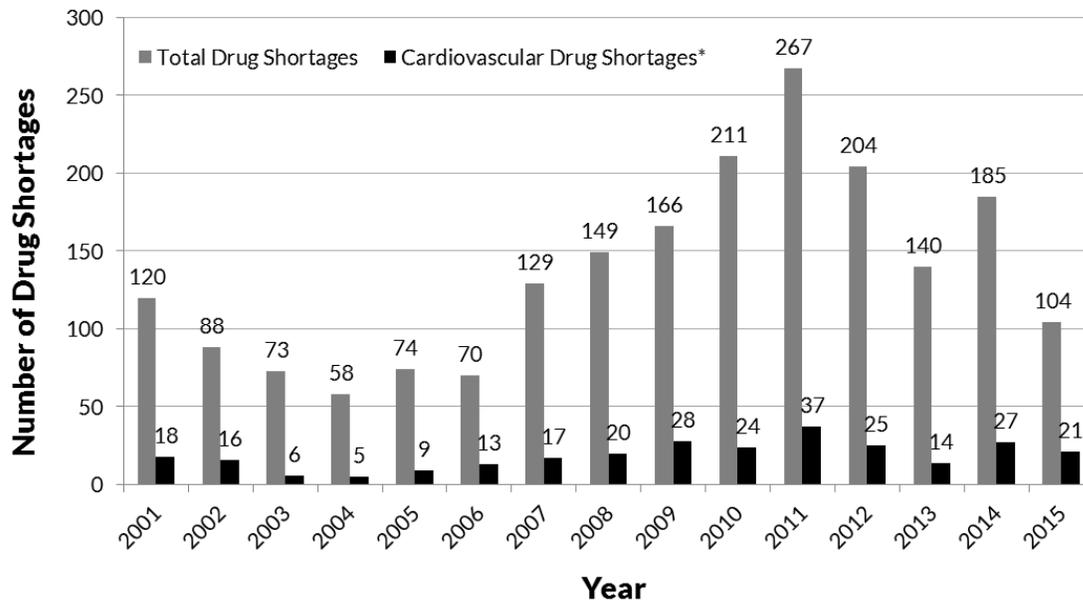
- Speak proactively on issues related to drug shortages and mobilize public support
- Utilize traditional (e.g., print, television, radio) and emerging media platforms (e.g., web, social media)
- Serve as media key contacts for health care organizations and professional societies

Advocate changes to laws and regulations that address the underlying causes of drug shortages.

- Develop a controlled-access clearinghouse for drug shortage information
- Implement metrics to incentivize and reward manufacturer reliability
- Require greater transparency in the drug manufacturing and distribution process
- Increase funding for efforts aimed at addressing drug shortages

**Abbreviations:** FDA – United States Food and Drug Administration

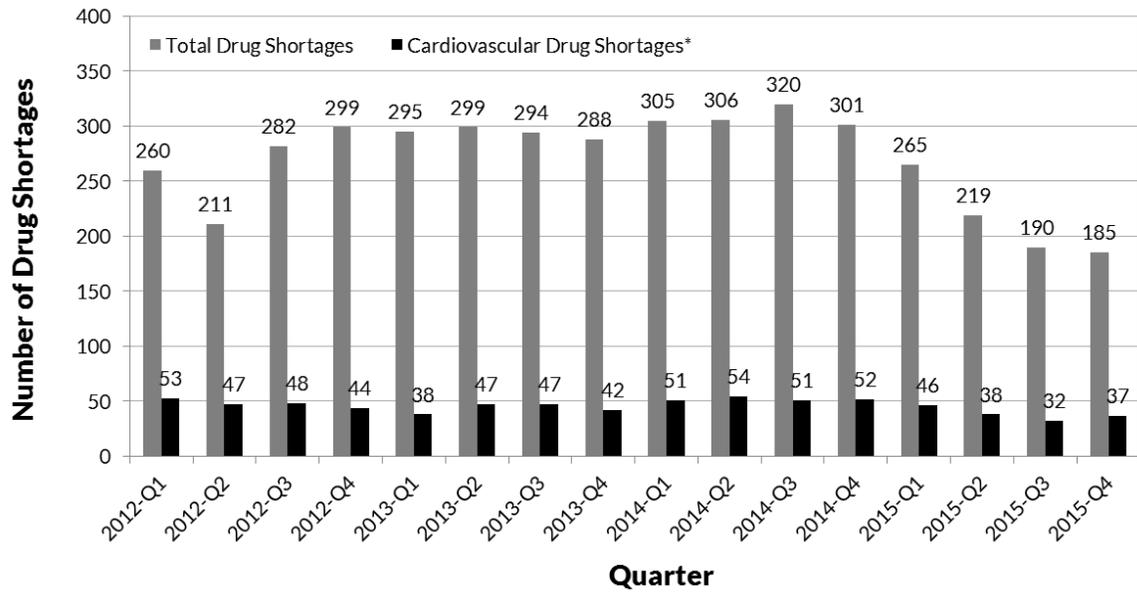
**Figure 1. New Drug Shortages from 2001 to 2015**



*\*Excludes intravenous fluids (e.g., sodium chloride 0.9%)*

*Data generated by the University of Utah Drug Information Service*

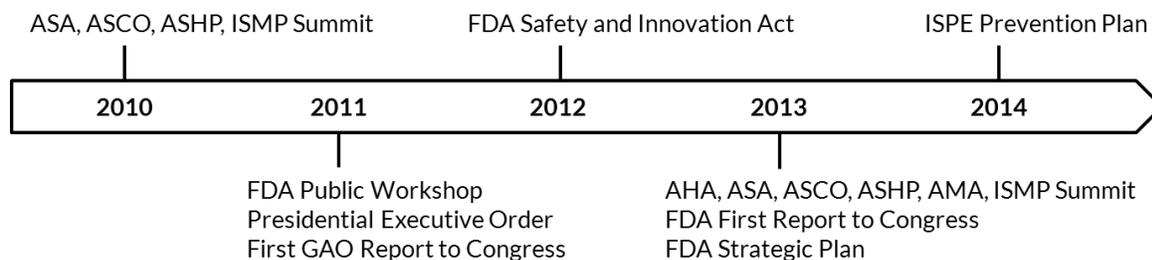
**Figure 2. Active Drug Shortages by Quarter from 2012-2015.**



\*Excludes intravenous fluids (e.g., sodium chloride 0.9%)

Data generated by the University of Utah Drug Information Service

**Figure 3. Timeline of Efforts to Prevent & Mitigate Drug Shortages**



**Abbreviations:** AHA – American Hospital Association; AMA – American Medical Association; ASA – American Society of Anesthesiologists; ASCO – American Society of Clinical Oncology; ASHP – American Society of Health-System Pharmacists; FDA – United States Food and Drug Administration; GAO – United States Government Accountability Office; ISMP – Institute for Safe Medicine Practices; ISPE – International Society for Pharmaceutical Engineering