

## The Shortage of Generic Sterile Injectable Drugs: Diagnosis and Solutions

By John R. Graham

### Executive Summary\*

According to the U.S. Food and Drug Administration, the number of times drugs were in short supply almost tripled from 61 in 2005 to 178 in 2010. The figure reached more than 250 in 2011. This means that manufacturers reported to the FDA that they were unable to meet demand for the drugs. Hospital and health-system pharmacists, as well as oncologists, anesthesiologists and other specialists have also increasingly reported difficulties acquiring drugs.

These are mostly injectable drugs for cancer and other important therapies, and they are frequently produced by generic drugmakers. These drugs are not dispensed by community pharmacies, but rather administered by health professionals in clinical settings. They differ from the medicines often sold as tablets in pharmacies in that they are manufactured from living things, such as bacteria. Because these injectable drugs can be infectious or poisonous in their natural state, they require a high degree of quality and care in their manufacturing, storage and distribution.

Shortage is not a permanent condition for any one of these drugs. Indeed, the absolute volume of prescriptions for the entire sample of drugs has increased in the past few years. Shortages occur for specific drugs in specific periods, but eventually get resolved. European markets do not appear to suffer from many such shortages, which are limited to the United States and Canada.

Although the problem is complex, the possible causes can be categorized as supply-side or demand-side. Supply-side

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\* Citations are provided in the main text.

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factors include physical constraints due to remarkably high standards in the chain of production and in the distribution of these potentially very dangerous products. Similar constraints apply to the acquisition of the drugs' active ingredients.

Another key supply-side factor is an unproductive FDA, which has increased its regulatory burden on current suppliers and made it very difficult to get approval for new generic medicines and manufacturing facilities. This regulatory overreach has likely reduced the ability of the supply chain to react to shortages. The evidence strongly suggests that these interventions are the major causes of the shortages.

Potential demand-side factors would include government-dictated rebates or discounts for programs such as Medicare, Medicaid, and the 340B program for safety-net hospitals and clinics. Many assert that these amount to price controls that make production unprofitable. While this view cannot be entirely discounted, the evidence that they contribute to the shortages is limited and weak.

Currently proposed solutions are unlikely to address the crisis satisfactorily. Congress appears ready to give more power to the FDA, initially by commanding drugmakers to notify the FDA six months in advance of an anticipated inability to maintain production. However, as noted above, the agency appears to be a major source of the problem. Making FDA regulations more onerous will not alleviate the current shortage of crucial medicines.

To expedite regulatory review, the generic pharmaceutical industry has lobbied to increase the FDA's budget with user fees paid by generic drugmakers. These user fees are almost certain to be legislated this year. They may improve the FDA's timeliness of reviewing new applications, but they are unlikely to result in long-term, systematic improvement. Instead, some of the increased revenue will be redirected by the FDA towards bureaucratic growth,

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after which its performance in approving new generic medicines or facilities will likely stabilize rather than continuously improve.

A more promising approach is defusing the problem by making it easier for competitors to enter the market in response to forthcoming shortages. Short term, American patients should be freed to use generic injectable drugs authorized by regulators in other developed countries, as long as they are so labeled.

Long term, the FDA's regulations on manufacturing should be limited to setting standards and measuring outcomes, rather than specifying every step of the manufacturing process. Instead of a bureaucratic monopoly, the FDA should be transformed into a "certifier of certifiers," permitting qualified third parties to approve new facilities and earn some of the user fees currently harvested by the FDA. This will increase the supply of crucial medicines, while lowering prices and better serving the well-being of all Americans.

There is a residual risk that government-dictated discounts on sterile injectable drugs will compromise supply by making it unprofitable to manufacture the medicine. This risk can be mitigated by developing a plan to shift the Medicare reimbursement for certain injectable drugs — especially for cancer — from the Medicare Part B program to the Part D program. In Part D, drugmakers negotiate terms with private insurers, rather than react to government-dictated prices. The private and competitive negotiations that occur under Part D are more likely to generate prices that adequately reimburse manufacturers while keeping Medicare expenditures under control.

## Introduction: The Drug Shortage Crisis

Since 2005, Americans have faced increasing shortages of key prescription drugs. The federal Food and Drug Administration reports that between 2005 and 2010 the number of drug shortages rose from 61 to 178 — nearly tripling. The figure leapt to more than 250 in 2011.<sup>1</sup>

This rise broke the positive trend of previous years. The number of shortages had dropped from 103 to 54 from 2001 through 2004.\*

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\* "Drug Shortages: FDA's Ability to Respond Should Be Strengthened," (Government Accountability Office, 2011), 16, <http://goo.gl/I1QzO> (accessed May 17, 2012). The shortage data are voluntarily reported by manufacturers to the FDA when they are unable to produce enough drugs to meet demand. Another source of data for drug shortages is the American Society of Health-System Pharmacists, which collaborates with the University of Utah to gather reports of shortages submitted via a website; see "Drug Shortages: Current Drugs," (American

The proportion of drugs suffering shortages is less than 1 percent of all drugs available in a given year.<sup>2</sup> The shortages, however, are concentrated in a vital category of medicines. According to the FDA, 74 percent of the 178 drugs in short supply in 2010 were sterile "injectable" drugs.<sup>3</sup>

These injectable drugs are used in important treatments for cancer and other diseases. The drugs are not sold in pharmacies, but rather administered by health professionals in doctors' offices, clinics and hospitals. They differ from the synthetically manufactured, small-molecule drugs usually dispensed as tablets by retail pharmacies in that they are not made from inert chemicals, but from living things, such as bacteria. In their natural state they can be infectious or poisonous. Therefore, manufacturing, storing and distributing these drugs demands significantly greater diligence and vigilance.

More than half the critical drug shortages reported between Jan. 1, 2009, and June 20, 2011, involved generic injectable drugs.<sup>4</sup> This is counterintuitive. A generic medicine is allowed on the market only after patents on the originally invented medicine that the generic copies have expired. Generic drugmakers are usually independent of the drugmakers that invented the drugs (the latter are known as "research-based" drugmakers). Generic drugs should thus be more readily available than patented drugs because competitors are free to market copycat versions, reducing prices.<sup>†</sup>

The IMS Institute for Healthcare Informatics, which has access to a proprietary database of pharmaceutical sales, analyzed the drugs listed as being in short supply by both the FDA and the American Society of Health-System Pharmacists as of Oct. 7, 2011. Remarkably, half of all generic injectable drugs were on the list.<sup>‡</sup>

So while the shortages may not appear important as a share of the entire portfolio of prescription medicines, they are certainly important to this segment. Two-thirds of the drugs were in five disease areas: oncology (cancer), anti-infectives, cardiovascular (heart disease), central

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Society of Health System Pharmacists), <http://www.ashp.org/DrugShortages/Current/> (accessed June 5, 2012).

† A generic drug producer's manufacturing processes are subject to strict regulation, however, a point that will be discussed in the main text below.

‡ "Drug Shortages: A closer look at products, suppliers and volume volatility," (IMS Institute for Healthcare Informatics, November 2011), 4. Because the analysis combined two lists that use different sources, the intersection of both comprised only 168 products.

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nervous system and pain management.<sup>5</sup> Last year, 550,000 cancer patients were treated with at least one of these medicines.<sup>6</sup>

Health professionals believe these shortages are likely harming patients. Premier Inc., an organization that purchases supplies for a group of health care providers, surveyed 311 pharmacy experts representing 228 hospitals and other providers during the second half of 2010. A full 89 percent reported that they had experienced a shortage that might have caused a safety issue or error in patient care, and 53 percent suggested that this had occurred six or more times. Further, 80 percent experienced a shortage that resulted in a delay or cancellation of a patient-care intervention.<sup>7</sup>

A previous 2010 survey of health care practitioners and pharmacists reported that one-third of respondents observed “near misses” and one-fifth reported adverse patient outcomes due to shortages.<sup>8</sup> Another 2011 survey of managers in 820 hospitals also reported a troubling frequency of drug shortages.<sup>9</sup> Nearly all hospitals – an astonishing 99.5 percent – reported one or more drug shortages in the last six months, and nearly half reported 21 or more.<sup>10</sup> These shortages have also disrupted randomized clinical trials for experimental cancer treatments because the patients assigned to the control groups supposed to receive the standard drugs could not get them.<sup>11</sup>

## The Sterile Injectable Drug Market

### A Concentrated Market

In order to diagnose the cause of the recent increase in shortages of sterile injectable drugs, we need to understand that the market is rather concentrated. According to the FDA, in 2010, the top five manufacturers accounted for 80 percent of the volume of drugs injected, and the top three alone accounted for 71 percent. Further, 342 of 569 sterile injectable drugs — 60 percent — were virtually single-sourced, with one supplier accounting for at least 90 percent of supply. With only six of the 569 drugs did the top two suppliers account for less than 50 percent of the supply.<sup>12</sup>

This leads to a lack of back-up capacity. Current oncology shortages are all due to three key manufacturing lines operated by two firms,<sup>13</sup> and this has long been the case.

There is a widely held belief that there has been significant manufacturing consolidation recently. This is unfounded.

Fewer than a dozen mergers occurred between 2005 and 2011, and these were small.<sup>14</sup> Indeed, in 2001 the top five manufacturers accounted for 90 percent of the market, and this market concentration has declined since then.<sup>15</sup> For generic injectable drugs overall, the number of manufacturer-drug combinations increased by 45 percent from 2006 through 2010. In every year, the number of manufacturers entering the market with a new drug exceeded those leaving it, and manufacturers have stated plans to increase capacity.<sup>16</sup>

Shortages are episodic, not permanent. The monthly volume of drugs injected for the entire set of 168 drugs identified by the IMS Institute for Healthcare Informatics as experiencing shortages last October has actually increased or at least remained stable over the last five years: from 55 million to 56 million standard units for injectables and 125 million to 157 million standard units for orally administered drugs.<sup>17</sup> Monthly sales increased from \$250 million to \$350 million over the period.<sup>18</sup> Thus, the average price per unit increased from \$1.39 to \$1.64. The volume of shipped sterile injectable oncology drugs increased by 14 percent from 2006 through 2010.<sup>19</sup> Almost all sterile injectable generic drugs used in the United States are manufactured domestically,<sup>20</sup> though foreign markets supply as much as 80 percent of the raw materials.<sup>21</sup>

The shortages derive from the limited number of suppliers of each drug. Even if the drugs have a stable supply over the longer term, market share changes dramatically in the short term, even month to month. This effect has increased markedly in the last year.<sup>22</sup> The most plausible explanation for these dramatic shifts in market share is that individual manufacturers are stopping production due to the supply-side issues discussed below.

Nor is the problem that generic manufacturers are having special difficulty gearing up to produce drugs newly available to them. On the contrary, most of the drugs experiencing shortages have been subject to generic competition for two decades: Almost 20 percent of reported shortages were for drugs introduced before 1980; just over half were for drugs introduced before 1990; and three-quarters, for drugs introduced before 2000.<sup>23</sup>

These shortages have led to a growing “gray market” of nontraditional distributors who compete aggressively to supply medicines when the traditional channel suffers a shortage. These distributors, unfortunately, often have very limited supplies, sometimes for just one or two patients at a time. Health-system pharmacists

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are skeptical about the quality of the medicines, especially because these distributors often do not offer a return or refund.<sup>24</sup>

A 2011 survey of 42 acute-care hospitals discovered that the average gray-market markup was 650 percent. The highest markup was 4,533 percent, and 10 drugs had markups greater than 1,720 percent.<sup>25</sup> Coping with shortages is an increasing burden. The time pharmacists spend managing shortages has tripled between 2004 and 2011, from two or three hours a week to nine.<sup>26</sup> Interestingly, the problem of shortages is almost uniquely American.

## **Sterile Injectable Markets Outside the United States**

Europe does not suffer consistent shortages of generic injectable drugs, although one example has been reported in the scholarly literature.<sup>27</sup> Some observers assert that this stable supply is because generics are deliberately priced higher there.<sup>28</sup>

Canadian policies, however, also support artificially high generic drug prices.<sup>29</sup> This has not prevented crisis in the provision of generic sterile injectable drugs, which has occurred because one supplier dominates. Sandoz Canada, the country's sole supplier of 140 injectable drugs, had to slow down production as a consequence of being accused of contamination by the U.S. FDA in November 2011. Although the FDA's Canadian counterpart did not cite the facility, Sandoz nevertheless decided to conform to the American regulations<sup>30</sup> to retain the option of exporting to the United States.

## **Supply-Side Factors in Shortages**

### **Physical factors**

Manufacturing and storing injectable medicines is difficult and costly, because they can be infectious or poisonous in their natural state. Exposure to heat and light needs to be managed in order to ensure that they remain sterile.<sup>31</sup> Experts generally agree upon many of the physical factors that contribute to these shortages:

- a disruption in the supply of raw materials
- an unexpected increase in demand
- natural disasters

- manufacturing capacity constraints
- lean inventory systems.<sup>32</sup>

The U.S. Government Accountability Office has noted that half of shortages due to manufacturing constraints were actually temporary shut-downs for improvements.<sup>33</sup> This helps explain why shortages of individual drugs are short-term. Shut-downs or slow-downs for unscheduled reasons include the discovery of bacteria or mold; the presence of inert foreign items like glass, metal or fibers in the vials; or the crystallization of the drug's active ingredient.<sup>34</sup>

However, it is not clear how these physical problems could have become significantly worse since 2005, leaving us to examine regulatory changes that might have exacerbated the shortages.

### **Regulatory factors**

Experts report that the FDA's slowness to approve new manufacturers or processes has dissuaded manufacturers from entering the market.<sup>35</sup> To be precise: New manufacturers are entering the market, but not enough of them are.

At a November 2010 summit, which included the American Society of Health-System Pharmacists, the American Society of Anesthesiologists, the American Society of Clinical Oncology and the Institute for Safe Medication Practices, it was generally agreed that the FDA's process for approvals for new generic drugs was too slow.<sup>36</sup>

The Generic Pharmaceutical Association reports that there is now a backlog of about 1,400 unapproved filings for generics at the FDA. However, it does not specify how many of these are for sterile injectable drugs. Median review and approval times have slowed to nearly 21 months, far worse than the legislatively mandated six months.<sup>37</sup> In 2005, the backlog was much smaller — only 891 applications — and the median time to approval was 16.3 months. The number of applications received that year was 766, increasing to 859 in 2009.<sup>38</sup>

Furthermore, in 2006, the FDA for the first time required drugmakers to seek permission to make so-called "pre-1938" drugs. These drugs were already in use before 1938, when the FDA — without the benefit of Congress amending the law — imposed its monopoly on approving prescription drugs for distribution. Since 2006, manufacturers have had to submit a New Drug Application demonstrating safety and effectiveness for

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pre-1938 drugs, as if the companies wanted to launch a completely new product.<sup>39</sup> This backlog means that it is increasingly difficult for competitors to enter the market if they anticipate a shortage developing.

It is unclear how frequently incumbent manufacturers stop production voluntarily and how frequently they do so in response to FDA orders when the agency perceives problems. When the FDA inspects a facility, it simply issues “Form 483” if it has questions or concerns not addressed during the inspection. Fewer than 640 Form 483s were issued in 2006, dropping to under 500 in 2008 and rising to about 650 in 2010.<sup>40</sup> Unfortunately, these numbers themselves are not helpful: We don’t know how serious each issue was.

We do know that the FDA has increased inspections of injectable-drug manufacturing facilities.<sup>41</sup> Experts assert that this increase in activity was largely caused by the 2008 recall of Chinese-sourced Heparin (a pre-1938 drug), which was associated with American patients’ deaths.<sup>42</sup> However, the FDA had failed to inspect the deadly source because the agency had confused the names of the Chinese plants that supplied the pig intestines from which the active ingredient was extracted.<sup>43</sup> So the FDA’s increase in inspections was caused not by an increase in dangerous activity at plants, but rather by the FDA’s own failure to maintain an accurate inspection schedule. We also know the FDA’s actions caused a facility in Canada to slow production, even though Canadian regulators thought it was safe.

The FDA’s warning letters are individually available, but it is not easy to digest them and understand the degree to which closing down of production lines is due solely to FDA action. Summary reports are few and far between. Even a March 2011 analysis by Bloomberg (reported from secondary sources) was merely able to conclude that 54 percent of manufacturing facilities inspected by the FDA in 2010 were cited for violations, up one-fifth from the low-water mark in 2007.\* This analysis covered all manufacturing facilities, however, not just those for injectable drugs. In addition, a technical violation can result in a number of possible remedies short of ceasing production.

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\* Silverman, Ed, “Which Drugmaker Fails Most FDA Inspections?”, *Pharmalot* blog (March 2, 2011), <http://www.pharmalot.com/2011/03/which-drugmaker-fails-most-fda-inspections/>. Mr. Silverman cites a Bloomberg study that is unavailable. At time of this writing, Mr. Silverman had not replied to the author’s requests for direction to the original study.

Furthermore, some of the drugs in shortage are also controlled substances, which are regulated by the Drug Enforcement Administration. If regulated by the DEA, the manufacturers cannot increase the quantity of the active pharmaceutical ingredient that they are making without seeking the DEA’s permission. However, there is no estimate of the relative importance of this factor.<sup>44</sup>

While various supply-side factors may be contributing to the increase in shortages, there is reason to believe from the evidence discussed here that the FDA’s regulatory actions are a major source of the problem. Specifically, the agency’s slower generic drug approvals, newly instituted regulation of pre-1938 drugs and increased inspections of injectable-drug manufacturers all suggest that FDA over-regulation is an important contributor to the shortages of generic injectable sterile drugs.

## Demand-Side Factors in Shortages

There are three major government interventions in the demand for these drugs: Medicare, the “340B” program and Medicaid rebates. Observers who believe that undue government control of demand is the primary cause of the problem focus on Medicare, because the program went through a significant policy change at the same time the shortages took a turn for the worse.

### Medicare

Since 2004, Medicare has reimbursed outpatient prescriptions through the “Part D” program. Medicare Part D’s costs have been significantly lower than initially budgeted, because the government does not fix the prices it pays for prescription drugs.<sup>45</sup> Instead, it contracts with a large number of private insurers, which offer Part D drug plans to Medicare beneficiaries. Private insurers win these contracts by bidding against each other in annual auctions. This is unique: Medicare Part A (for hospitals) and Part B (for physicians) use government-dictated prices to reimburse providers.

Injectable drugs fall under the Part B program, because doctors buy them. In 2005, Medicare stopped reimbursing doctors using a benchmark called “average wholesale price” and switched to a figure called “average sales price.” This is because the AWP (which market insiders referred to as “Ain’t What’s Paid”) was a fictional price quoted by drugmakers, unrelated to actual wholesale transaction prices. The AWP was also the benchmark for very large payments from drugmakers to doctors. Medicare Part B reimbursements were set at

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95 percent of AWP in 1998 and reduced to 85 percent of AWP in 2004.

These reimbursements, however, bore no relation to the “spread” that a physician (especially a cancer specialist) earned from the drugmaker. For example, a physician might receive an invoice from a drugmaker for \$100 — the AWP — which he would forward to Medicare for a reimbursement of \$85. He might also receive a “spread,” though, of 50 percent (or \$50) back from the drugmaker. Thus, he would make a lot more than a casual observer (or taxpayer) would expect — a process called “selling the spread.”

The average sales price used in Medicare now is an average of actual net sales. The reimbursement to the doctor from Medicare is 106 percent of the ASP.

This change had a dramatic impact on medical oncologists (cancer specialists), whose practice largely consists of injecting drugs (chemotherapy). A 2005 survey of more than 2,000 drug codes found that the ASP is 49 percent less than the AWP. For a sample of over 1,000 generic drugs, the ASP was 68 percent less than the AWP.<sup>46</sup>

Clearly, injecting drugs became less profitable for physicians, especially cancer specialists.\* But would the same be true for drugmakers? One scholar has developed a highly theoretical model that shows that the AWP to ASP change could have contributed to drug shortages, because it increased the difference between what private insurers pay and what Medicare pays. According to this model, each 10 percent of market share accounted for by Medicare is associated with an increase of shortage frequency of 7.5 percentage points.<sup>47</sup>

But actual history does not support this theoretical model: The volume of generic injectable cancer drugs in Medicare Part B increased by nearly 30 percent in 2006 through 2010, while the volume of injectable cancer drugs overall, as noted, increased by just 14 percent. Only 10 percent of the volume of Part B injectable drugs in 2006 and 2007

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\* If anything, the change in reimbursement should have led to a reduction in the number of medical oncologists practicing. Ali Yurokoglu, “Medicare Reimbursements and Shortages of Sterile Injectable Pharmaceuticals,” (Graduate School of Business, Stanford University and NBER, 2012), 9, <http://goo.gl/fV/kH2> (accessed June 12, 2012). Evidence of this is weak. Advocates for the specialty assert that a shortage is developing. The Community Oncology Alliance states that there have been 199 clinic closures and 369 practices struggling financially since early 2008. Three hundred and fifteen clinics have been acquired by hospitals and 111 have merged or been acquired by a corporate entity. But the report did not conclude that oncologists themselves have quit practicing. Zosia Chustecka, “Community Oncologists Not to Blame for Drug Shortages,” ([www.medscape.com](http://www.medscape.com), 2011), <http://goo.gl/iptdS> (accessed June 12, 2012). (Available with free registration.)

consisted of drugs that experienced shortages during the next three years.<sup>48</sup> The evidence continues to suggest that shortages are a result of supply being unable to meet increased demand, not too much demand caused by artificially low prices dictated by government.

Nevertheless, the change in the benchmark does really change the incentive for medical oncologists to view their drugs as a profit center, so it might not be surprising that the reform would have motivated them to use more drugs — that is, to make up in volume what they lost in the spread. Two physicians have proposed dramatic reform that would pay physicians an administrative fee to inject drugs, thereby reducing any perverse incentive.<sup>49</sup>

## The 340B program

The federal 340B program mandates that drugmakers sell drugs at discounted prices to so-called “safety-net” hospitals and clinics, which disproportionately serve low-income communities. The program results in discounts ranging from 20 percent to 50 percent, according to HRSA.<sup>50</sup> The Patient Protection and Affordable Care Act (PPACA), also known as Obamacare, has significantly increased the number of hospitals eligible for the 340B program, which demands deeply discounted prices for safety-net providers.

In 2002, about 8,000 hospitals and clinics were participating; by 2010, more than 14,457 were participating.<sup>51</sup> As of July 2011, more than 16,500 covered entities were enrolled.<sup>52</sup> However, 340B providers have not reported shortages except in two cases: intravenous immune globulin; and when the 340B price drops significantly. In the latter case, 340B providers are able to order significantly more of the drugs at below-market prices — prices at which the manufacturers would be unwilling to supply the drugs absent the government mandate.<sup>53</sup> It is reasonable to conclude that this government price intervention would create a perverse incentive for drugmakers to ration supplies to 340B facilities. The intervention would not, however, induce manufacturers to stop producing overall.

Also recall that while the 340B program demands a discount, it does not fix nominal prices. Drugmakers can respond to an increase in the government-dictated discount (or increase in number of beneficiaries of the discount) by increasing prices to private health insurers.

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## Medicaid

Medicaid, the joint state and federal program for low-income residents, also demands discounts. Medicaid discounts — 13 percent for generics — are calculated off the “average manufacturers’ price.”<sup>54</sup> The AMP is similar to ASP but redefined as recently as 2010 for injectable drugs.<sup>55</sup>

Nothing in the literature reviewed for this study suggested that health care providers who are experiencing shortages of injectable drugs blame Medicaid reimbursement for the crisis. It may be that they avoid seeing patients enrolled in Medicaid, which would be consistent with research, although it condemns those patients to poor quality health care. A recent study of five-year cancer survival rates for Ohio residents concluded that Medicaid patients experienced significantly worse outcomes, with a mortality rate half again as bad as the non-Medicaid population.<sup>56</sup> A large and growing body of evidence indicates that physicians limit their availability to Medicaid dependents.<sup>57</sup>

It is not clear, however, that this contributes to drugmakers’ cutting off supply. As in the 340B program, government intervention takes the form of dictated discounts, not nominal prices. So drugmakers could respond by increasing prices to private payers.

## Assessing Demand-Side Explanations

Government intervention in setting prices might have some impact on drugmakers’ willingness to produce generic injectable drugs. The evidence is not convincing, however, especially considering the episodic nature of the shortages. If government intervention in pricing were the dominant cause, we would expect to see suppliers quit the market for good, not just clean up their manufacturing and re-enter.

Nevertheless, this conclusion must be tempered with the observation that neither the FDA nor the American Society of Health-System Pharmacists has reported shortages of Botox®, the most well-known generic sterile injectable drug. Most Botox is paid for directly by patients and free of government intervention in price-setting.

## Current Proposals and Political Response

### The Administration and Congress

President Obama proposes to fix this problem by requiring drugmakers to notify the FDA six months — half a year! — before a shortage occurs. He has already taken steps in this direction. In October 2011, the president issued an executive order recognizing that shortages are becoming more severe and frequent.<sup>58</sup> The order claimed, “[T]he root problems and many of their solutions are outside of the FDA’s control,” but nevertheless demanded that the FDA:

1. increase the burden on manufacturers to notify the FDA of forthcoming shortages;
2. expedite the regulatory review of new drug suppliers and facilities;
3. tell the Department of Justice when it suspects stockpiling or price gouging (“exorbitant prices”).<sup>59</sup>

In February, the FDA issued preliminary guidance explaining how it would execute these new responsibilities. The new guidance appears to push the limits of FDA administrative powers over manufacturers.<sup>60</sup> Current law mandates that only a “sole manufacturer” of drugs that are “(A) life-supporting; (B) life-sustaining; or (C) intended for use in the prevention of a debilitating disease or condition” is required to give the FDA six months’ warning of an impending shortage.<sup>61</sup> The assumption seems to be that if the FDA knows about a potential shortage, it can then fix the problem.

The recent guidance clearly calls upon all the FDA’s considerable powers to motivate manufacturers to report voluntarily all forthcoming shortages. The guidance encourages manufactures to be “over-inclusive” in defining these terms.<sup>62</sup> “Discontinuance,” which used to mean permanently ceasing production, now includes temporary stoppage (if it will disrupt supply).<sup>63</sup> The FDA appears to acknowledge that manufacturers cannot always predict six months in advance and provides for short-term warnings in certain urgent situations.<sup>64</sup>

Legislating this expansion of FDA power by giving the FDA clear authority to demand a six-month notice from all drug makers is a current political priority. As of this writing, the Prescription Drug User Fee Act renewal legislation, which is poised to pass Congress with an overwhelming majority, contains this provision.\*<sup>65</sup>

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\* This is called the Food and Drug Administration Safety and Innovation Act.

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Both the president and Congress are influenced by a recent analysis produced by the U.S. Government Accountability Office. The analysis concluded that the FDA does not yet have a systematic way of gathering data on shortages, but rather just maintains individual files that are not reliable, easily retrieved or routinely recorded.<sup>66</sup>

Despite this inability to execute basic record-keeping that can provide useful information, the FDA asserts that early notification, even as narrowly practiced today, has allowed it to respond by expediting review of new products for approval or exercising regulatory flexibility.<sup>67</sup> The FDA asserts that early warnings helped it to mitigate 23 injectable-drug shortages in 2006, and that this increased steadily to 132 in 2010.<sup>68</sup> In February, the FDA asserted that it had prevented 114 shortages just since last October's executive order.<sup>69</sup> In May 2012, six months after the President's executive order, the FDA claimed to have prevented 128 shortages in that half year. It also claimed that 42 new drugs were reported in shortage in 2012, versus 90 at the same time in 2011.<sup>70</sup>

These claims of shortages "prevented" have not been independently verified.

## Expert Parties

Most of the proposals already made by subject-matter experts pretty much go along with those the president and Congress are entertaining. First and foremost, they want to legislate that drug makers give a six-month warning to the FDA before a shortage occurs.

Experts note that shortages are "occurring in an environment that is characterized by a near absence of communication between drug manufacturers and the FDA," because the FDA cannot always force manufacturers to give early warnings under its current regulatory powers.<sup>71</sup> Pharmacists and doctors are frustrated that they do not see these shortages coming and do not know how long they will last.<sup>72</sup>

The American Society of Health-System Pharmacists, the American Society of Anesthesiologists, the American Society of Clinical Oncology, and the Institute for Safe Medication Practices have generally agreed that the FDA's lack of power to compel notification from manufacturers is a significant contributor to shortages.<sup>73</sup> The American Society of Health-System Pharmacists recommends increased FDA power to require notification from manufacturers, especially manufacturers of single-source products. These notifications could be confidential.<sup>74</sup> The confidentiality clause would reduce the risk of hospitals

and doctors hoarding the drug in question, but this precaution would not really be a solution to the shortage.

The Generic Pharmaceutical Association proposes that an independent third party, among other things, gather the information on forthcoming delays, a mechanism the trade association calls the "Accelerated Recovery Initiative."<sup>75</sup> The GPhA also supports another legislative measure that might have an impact on the supply of generic drugs, including injectable drugs: the adoption of user fees, payable to the FDA, to fund new approvals of generic drugs and manufacturing facilities. This system is likely to be legislated in the renewal of the Prescription Drug User Fee Act, which the GPhA endorses with an offer to support a five-year levy against its members of \$299 million in user fees.<sup>76</sup>

This would be the first time that the generic pharmaceutical industry has been charged user fees by the FDA (the research-based pharmaceutical industry has paid user fees to the FDA for two decades). GPhA believes that by offering to fund the FDA with its members' user fees, the approval process for generic drugs — currently severely blocked — will become faster.

## Recommendations

A mandated six-month warning would allow the FDA to engage in some sort of mitigation efforts, but there are potential risks, too. Half a year seems to be a very long lead-time. FDA action could send a signal that would prompt hospitals and other providers to hoard. Likewise, if a drug maker is nervous about being punished for not giving a six-month warning, he could "cry wolf" and simply notify the FDA every six months that he is going to shut down. On the other hand, a drug maker might choose to withhold discontinuance information and suffer FDA fines rather than expose his market share to competitors. It is far from clear that this increase in regulatory power would improve the quality of information about forthcoming shortages.

Nor is it credible that the FDA will substantively improve its approval of new generic suppliers. The current shortage of sterile injectable drugs, after all, took place on the FDA's watch. It hardly follows that legislation giving the FDA more power over drug makers will alleviate the current shortage of crucial medicines. One purpose of early notification would be to prompt the FDA into accelerating its approval process. But the FDA has good reason to do that already, knowing that the shortage of sterile injectable drugs is harmful to patients.



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Furthermore, the generic pharmaceutical industry should not be over-enthused about the opportunity to pay user fees to accelerate regulatory approval. The experience of the research-based pharmaceutical industry is that such payments do have an effect, but some of the FDA's extra income soon gets transformed into bigger bureaucracy, and the actual regulatory output does not continuously or consistently improve.\*

These observations lead to several recommendations, mostly targeted on the supply side.

- 1. Limit the FDA's power to compel advance warnings.** Legislators should be very skeptical about increasing the FDA's power to compel manufacturers to give a six-month advance warning of forthcoming shortages. This mandate is likely to confuse the issue more than clarify it.
- 2. Be cautious in the adoption of user fees for FDA approval.** The generic drug industry should not assume that increasing the FDA's revenue will improve its performance continuously. Twenty years of experience with user fees for regulatory review of innovative patented drugs shows that such improvement is maintained only by constantly increasing funding to the FDA.
- 3. Allow informed use of non-FDA-approved sources from developed countries.** As the author has recommended in another recent study, if people in other developed countries can use drugs not approved by the FDA, American doctors and patients should be free to use drugs from those manufacturing facilities as long as it is disclosed that they are not FDA-approved.<sup>77</sup> Consider the example of the Sandoz plant in Canada, which is in compliance with Health Canada's regulations.
- 4. End the FDA's monopoly over drug certification.** Congress should define a long-term goal of moving the FDA away from a regulatory monopoly to a "certifier of certifiers," allowing qualified companies to investigate and approve drugs and drug manufacturers for legal entry into the health care market. This would increase regulatory capacity with private-sector third parties that would have far better incentives to deliver cost-effective quality assurance than the FDA does. Such private certifiers already exist, from Underwriters'

Laboratories, which certifies tens of thousands of products in areas such as fire safety, to the Snell Memorial Foundation, which certifies helmets for bicycling and other sports.<sup>78</sup>

This arrangement would speed market entry by drug suppliers, including entrepreneurial generic manufacturers that would invest in market research to inform them when to ramp up production in anticipation of a forthcoming shortage. This would result in much better systemic redundancy than increasing the regulation of incumbent suppliers, as recommended by the Obama administration and (unsurprisingly) the incumbent suppliers themselves. Furthermore, because the third-party certifiers would focus solely on quality of output, not processes, drug makers would be more likely to differentiate themselves by innovating new manufacturing technologies.

- 5. Move sterile injectable drugs to Medicare Part D.** Although this analysis concludes that demand-side causes of the shortages are likely not critical, they cannot be entirely discounted. Medicare, especially, experienced a major change in reimbursement around the same time that shortages started to increase.

Fortunately, the Medicare Part D program shows a way to eliminate the risk that the government-dictated pricing mechanism in Medicare Part B will harm access to injectable drugs. By moving injectable drugs from Part B to Part D, where drug makers negotiate prices with private insurers, the federal government will save money and ensure that prices for these drugs more closely reflect their value. Because physicians should be paid based on their services, rather than how many drugs they administer, it is likely that moving certain injectable drugs, especially cancer medicines, to Part D would result in innovative payment models. Indeed, at least one private insurer has announced an effort to pay cancer specialists for outcomes, rather than injecting drugs.<sup>79</sup> It should be relatively straightforward for insurers to employ such innovative payment mechanisms once certain injectable drugs are moved to Medicare Part D.

Reducing shortages of generic injectable medicines is a worthy goal. To achieve this goal, U.S. policy should reduce the FDA's power, expand patients' freedom to use generic injectable drugs from additional sources and encourage entrepreneurs to enter the market faster with innovative production techniques. ❧

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