

Statement before the Committee on Oversight and Government Reform
Subcommittee on Healthcare
On November 30, 2011

The Causes of Drug Shortages and Proposals for Repairing these Markets

Scott Gottlieb, MD
Resident Fellow
American Enterprise Institute

Washington, DC

The views expressed in this testimony are those of the author alone and do not necessarily represent those of the American Enterprise Institute.

Introduction

Mr. Chairman Issa, Mr. Ranking Member Cummings; I want to thank you for the opportunity to testify today before the Committee on Oversight and Government Reform, Subcommittee on Healthcare, on the shortages of critical sterile injectable and infused drugs.

The problems have affected mostly older parenteral drugs that are sold as generic medicines. These drugs are typically sold at low prices for slim profit margins. The cost of manufacturing them often comprises a sizable proportion of the overall price of the finished drug. More than 200 sterile injectable drugs are on the current shortage list kept by the American Society of Health-System Pharmacists.^{i ii}

While other countries are also experiencing drug shortages,ⁱⁱⁱ in the U.S. the critical medicines that are in scarce supply, and the protracted nature of the underlying problems, make our situation uniquely challenging. The shortages have caused patients to miss or delay chemotherapy or to get inferior antibiotics, anesthetics and intravenous nutrition. Shortages of drugs have triggered clinical mistakes and bad outcomes in situations where patients received medicines that prescribers weren't accustomed to using.^{iv} Hospitals are being forced to ration key medicines and patients forced to sit on waiting lists for vital drugs.^v

Some blame these shortages on the "manipulation" of drug middlemen. These "gray market" distributors have become an unofficial alternative market for drugs -- operating outside the usual distribution networks. This shadow market has exploded in recent years, with vendors charging markups of up to up to 3000% for some cancer drugs.^{vi} These vendors stockpile supplies to be redistributed later at high prices, once shortages arise.

While unpleasant, the existence of this gray market is not the trigger of shortages but one of its consequences.^{vii} Neither is the lack of qualified manufacturers for these generic sterile injectable drugs itself a primary cause for the shortages.^{viii} Here again, the lack of qualified manufacturers is another symptom of the underlying problems. After all, branded drugs typically have only a single manufacturer, and aren't facing the same production problems. Under the right circumstances, a handful of adept companies can supply these markets.

In our search for the cause of the shortages, and the pursuit of solutions, we need to be careful not to confuse the consequences of the problems for its root causes.

The reality is that the causes for these scarcities can be complex and multifactor. Each episode typically has unique characteristics that make it distinct from other drug shortages. This makes finding policy solutions challenging. There are, however, some common problems that are -- to varying degrees -- threaded through each of these episodes. I believe these common factors should be the focus of our attention. They provide the most logical place for policymakers to start addressing the root causes of these drug shortages.

I group these common factors into three categories:

The first are regulatory challenges that have made the manufacturing of these products safer and more reliable, but also in some cases more challenging and expensive.

The second are mechanisms that make prices sticky, limiting profitability and precluding new investment in additional supply and better and more efficient manufacturing.^{ix}

The third and final category is market structures that prevent firms from branding their products, and reflecting by how they price them, legitimate improvements in manufacturing that allow drugs to be produced more reliably and in scalable facilities.

Regulation of Drug Manufacturing

The first challenge is the way the manufactures of these drugs are being regulated. In recent years, the Food and Drug Administration (FDA) has gotten tougher on potentially dangerous snafus that have long plagued the production of some injectable generic drugs. These include problems with sterility, and particulate matter getting into the solutions.

Consider these statistics: In the early part of the last decade, FDA prompted the recall of about 45 injectable drugs a year. Annually, about five of these recalls related to particulate getting into the formulations. This included things such as metal shavings from corrosion or abrasion in the manufacturing process, glass from delamination, or crystals of drug substance. In the last few years about 100 injectable products each year have been recalled. Between 20 and 30 of these recalls were the results of particulate found in the solutions.^x

Even if the incidence of these problems is on the rise, it's likely that better oversight is also prompting more recalls. FDA is catching more of these problems, triggering more recalls.

Take the example of more glass lamellae being found in solution. Through 2010, firms typically recalled no more than a single product for this kind of deficiency. By the end of the second quarter in 2011, there had been 21 products recalled for glass lamellae being found in drug solutions. This surge in recalls was primarily due to a single decision by a number of different firms to simultaneously switch to packaging their drugs in lower-cost vials that degraded under certain conditions. But the episode speaks to a lot of the problems plaguing the market for sterile injectable drugs. That these problems were spotted quickly suggests that FDA's detection methods have improved. In a previous era, this might have evaded scrutiny longer. That the firms switched to these cheaper vials suggests that there is a lot of pressure to lower the costs of these goods, creating the opportunity for new risks.

Now just because some manufacturers have long produced to lower standards doesn't mean FDA should continue to ignore legitimate problems. The FDA has real concerns about the integrity of how some of these drugs are manufactured. Contribution to the finished solution from equipment, process, components, and packaging should never be considered acceptable. In the past, FDA may have lacked resources to apply strict standards to manufacturers (especially those products made at foreign sites).^{xi} But the fact is that there has been a fairly rapid tightening of the regulatory scrutiny of these products over a short period of time. To the degree that the market for these products was already populated with older-line, less nimble, less well-capitalized manufacturers; that increased regulation has caught them off guard. Low margin producers can't easily meet higher standards.^{xii}

The regulatory scrutiny isn't the cause of shortages, but another of the multiple factors that have contributed to the conditions challenging these drug makers.^{xiii} With its vigilance

heightened, the FDA has required manufacturers to undergo major plant renovations, suspend facilities or stop shipping goods from suspect production lines. The FDA and the manufacturers often don't understand the drug-production processes well enough to detect the root cause of problems. Instead of calling for targeted fixes of troubled plants, the agency has often required manufacturers to undertake costly, general upgrades to facilities. As a result, in 2010, product quality issues -- and the subsequent regulatory actions taken by FDA to address these problems -- were involved in 42% of the drug shortages.^{xiv}

The regulatory oversight of manufacturing processes shouldn't be scaled back just because it's chasing some substandard manufacturers out of the market. But we need to take measure of the impact these standards have on the cost of manufacturing the drugs. If we want to maintain high standards, we need policy measures to accommodate the economic impacts.

This begins with making sure the regulations governing drug manufacturing, FDA's Good Manufacturing Practices (GMPs), are as efficient as possible. Manufacturers have long complained that these policies are outdated, and at times inflexible. The general refrain is that it's too hard for producers to upgrade manufacturing facilities without drawing inordinate scrutiny from regulators. This has resulted, at times, in outmoded production methods persisting because product developers concluded -- rightly or wrongly -- that it was too hard to get approval to incorporate better manufacturing technologies into plants.

FDA has undertaken a broad effort to implement new GMPs. But it made mostly modest changes. Drug companies have cited examples where the FDA requirements were so out of date that they maintained two facilities -- a modern plant next to an older facility, one making drugs for the European Union and rest of the world, and the older plant to meet FDA's out-of-date requirements. While branded drug companies can afford to do that, or to invest in the long process to stand up new facilities while still maintaining their older plants, the manufacturers of lower margin generic parenteral drugs often cannot. Generic manufacturers estimate that it can take as long as seven years, from start to finish, to stand up a new manufacturing facility for sterile injectable drugs. The divergent, and sometimes outdated specifications required by FDA is one reason why we see a number of drug makers manufacturing their generic parenteral products only for sale outside the U.S.

Policy makers have suggested that one way to alleviate the U.S. shortages is to import drugs manufactured for other markets. Rather, I believe the question we should be asking is why the companies making these drugs aren't choosing, on their own volition, to market these drugs inside the U.S. in the first place. Pricing is certainly one factor. Companies can often charge more for the generic parenteral drugs when they sell these medicines in Europe. But regulation is also a factor. In some cases, the newer facilities that these drugs are being manufactured in haven't met FDA clearance. Bringing our regulatory standards up to date, making it easier for manufacturers to adapt plants with new technologies, and harmonizing GMP requirements across different established markets like Europe would better enable manufacturers to enter the U.S. with reliable supplies. All of these elements should continue to be part of FDA's efforts to modernize its approach to GMPs and address the shortages.

Another regulatory issue at play in these shortages relate to the backlog that FDA currently has for generic drug manufacturing supplements. The FDA expedites the review of supplements related to shortage drugs, so the backlog doesn't directly affect these products.

But the agency's expedited review often kicks in only once drugs approach shortage status. For the rest of the almost 3,000 supplements that are on backlog, these applications can sit for months and sometimes years owing to a lack of resources to enable their timely review.

While I have no direct knowledge of the flow of FDA's queues, it seems almost inevitable that some of these backlogged manufacturing supplements (requests of FDA to allow a company to either improve existing facilities or stand up new plants) sat in this backlog while the drug approached the precipice of the shortage list. In other words, FDA's prioritization of supplements only kicks in once a drug is judged to be at or near shortage. What about drugs that approached shortage long after new facilities couldn't be stood up? The correlation between the regulatory action and the shortage may not be obvious, but we should explore whether some of the drugs on the shortage list had supplements that were at one time delayed because the resources didn't exist at FDA to enable their timely review.

The backlog in reviewing manufacturing supplements can add as much as a several year delay to approval of those manufacturing changes. Often these supplements are requests to expand or modernize manufacturing facilities. The delay in reviewing these supplements can have significant economic implications. For example, to submit these applications, companies may also have to manufacture three commercial batches with the new manufacturing process while still running the old manufacturing and only selling the old batches. The backlogs are now so long the new batches may become worthless by the time the new manufacturing facility is approved. The financial burden to the generic drug manufacturers of having to waste these first-run batches is a huge disincentive to modernize.

FDA's position has been that without additional resources, they cannot hire a sufficient number of chemist-reviewers to solve the problem. Resources are certainly a large part of the issue. To these ends, the proposal for a Generic Drug User Fee program should provide the agency with the additional money that's needed to tackle this backlog.^{xv} Congress should look to build into this legislation specific constructs that allow FDA to prioritize resources to the review of supplements related to the manufacture of generic sterile injectable drugs -- not only those drugs that are currently in shortage but all of the generic parenteral drugs. That way we will not only tackle current shortages but also better avoid future ones.

Regulation of Drug Pricing

The greater regulatory scrutiny presents a more immediate challenge also because of the way these generic parenteral drugs are reimbursed by Medicare and many private payers. The current system prevents manufacturers from adjusting prices to reflect higher cost of goods as a result of the manufacturing upgrades that they are required to undertake.

A 2003 law sets the price Medicare will pay for physician administered drugs to an "average sales price" that is at least six months old at any given time. This flawed concept means even if a generic firm raises its price to reflect increased production costs, Medicare won't immediately pay the new price until approximately six months later. As a result, purchasers (mostly hospitals and in some cases individual physicians) lose money on these drugs for months at a time since the price they pay for the drug could be significantly higher than the historical price that Medicare reimburses for the medicine. Since many of the manufacturers producing these parenteral drugs do so in order to win group purchasing contracts with

larger institutions like hospitals, and already view these drugs as “loss leaders” that allow them to get more lucrative contracts for other medicines, they’re reluctant to raise prices to match rising production costs if it means leaving customers in a financial pinch. The easier path for these manufacturers is to cease production of these individual medicines.^{xvi} Because the margins in this space (and profits from incremental sales) are slim, and there are few penalties for shirking contracts, there’s little incentive for maintaining redundant capacity.

In order to make the long-term, capital intensive investments needed to bring on new manufacturing capacity for these parenteral drugs, generic firms would need to know that they can take, and sustain, price increases over a reasonable period of time. It should come as no surprise that a recent analysis by the Department of Health and Human Services found that among the group of drugs that eventually experience a shortage, average prices decreased in every year leading up to a shortage. The mean price decrease over these periods leading up to the shortages averaged of as much as 27%. By comparison, the average prices of drugs that were never in shortage over this period, in most cases, rose slightly.^{xvii}

The bigger issue with the way Medicare reimburses these drugs, however, is the way it sets a single, flat price for each broad category of medicine rather than paying for these drugs individually. Medicare assigns a single “billing code” to each category of medicines. The agency then establishes a single rate that it will reimburse for each code. That rate reflects the average price of all of the drugs in a particular category of medicines. That means that even if a drug has multiple manufacturers, some better than others, all of the drugs in a particular category will be paid the same average rate. In other words, the drugs are treated like commodities by CMS. The reimbursement level is the same for every drug in a billing code regardless of whether a particular manufacturer has been subject to more stringent regulatory oversight in recent years or has invested in upgrading its manufacturing processes.

Since FDA’s enforcement of these facilities is often uneven at any given time, one particular manufacturer might be facing significantly higher manufacturing and regulatory costs while other drug producers in the same category are still getting by with older, cheaper, and perhaps less safe facilities. By lumping all of the drugs into the same billing code, it creates a race to the bottom on the cost of goods, with the price paid for the entire category influenced by the lowest cost producer. This race to the bottom on manufacturing costs can work reasonably well in producing significant savings when it comes to products that are easy and cheap to manufacture, like small molecule drugs (pills). But it creates significant risks in markets like sterile injectable drugs, where the manufacturing is not a trivial affair and a constant drive to lower costs can mean necessary manufacturing safeguards are being forgone. Certainly this race to the bottom creates significant disincentives to making any manufacturing upgrades that would end up raising the cost of goods.

The result of these policies is that generic prices can’t rise to reflect changing demand or the need for bigger investments in manufacturing. Branded parenteral drugs have faced similar production and regulatory issues. These drugs are also paid for under the same flawed “ASP” scheme. But the branded drugs have larger profit margins to offset the cost of plant upgrades. The generic parenteral drugs are already being sold at slim profit margins, and sometimes for a loss. Any capital requirements for investments in new manufacturing equipment and production facilities are hard to recoup given the way Medicare pays for these drugs. When the slim profit margins of the generic drugs become eroded by the cost of

upgraded production facilities, more and more manufacturers are choosing to exit product lines entirely rather than invest money to meet steadily higher standards.

Some have suggested that the ASP construct is behind these shortages through its impact on clinical prescribing.^{xviii} According to this argument, doctors receive a financial incentive to prescribe the highest priced drugs because of the 6% spread that they earn for administration of agents. As a result, it is argued, when higher-priced versions of drugs come along, they switch away from cheaper generics.

But this argument, even if true, is a non sequitur. It still doesn't explain why the generic markets can't be adequately supplied. Even if demand diminishes as a result of branded competition for a generic medicine, the fact is that the current manufactures are still not keeping up with the now reduced demand. Under this argument, the price is used to help explain the demand. But it doesn't take any measure of the supply side of the equation. Even if demand for these drugs diminishes over time, if the market was healthy, if prices could adjust for supply, and if profits could be earned, there would be manufacturers willing to step in to supply the need for these generic medicines, even at newly reduced levels.

Proposals for Reform

To fix the problems with inadequate supply for generic sterile injectables, we should lift existing price controls when it comes to critical injectable drugs that are generic, and take steps to provide manufacturers with incentives for making improvements in the manufacture of these drugs that can lead to a more stable supply and more scalable production facilities.

First, Medicare should ditch the flawed "average sales price" when it comes to generic sterile injectable drugs and reimburse manufacturers according to the price paid by wholesalers on the open market. This wholesale acquisition cost (WAC) is already collected and reported to Medicare. Reimbursing the parenteral drugs according to WAC would allow generic firms to more quickly adjust charges to match rising production costs and meet demand.

These drugs should also get a holiday from other Medicaid price-control schemes that serve to distort market prices and reduce profitability and incentives to invest in new production. These include constructs such as Medicaid Best Price rules, the 340B drug discount program, and other mandatory rebating schemes.

Medicare can also allow these drugs to have individual billing codes, rather than paying for each class of drug according to the same billing code. This would allow manufactures to price their drugs individually. It would help to eliminate the race to the bottom on pricing and, in turn, cost of goods. If manufacturers made legitimate improvements in their manufacturing to enable more stable supply, they could try to represent these improvements in contracting discussions to secure better pricing. Some purchasers might well be willing to pay for supply that's produced from more up-to-date and reliable facilities. Providers are becoming increasingly conscious of how and where drugs are manufactured. Allowing drugs to have individual codes would let manufacturers price products to reflect these attributes.

Finally, we should consider policy constructs that would give manufacturers a financial incentive to develop intellectual property that improved the manufacturing characteristics of

generic medicines even if these changes it didn't change the clinical properties of a drug. We could establish criteria for which manufacturing improvements are believed to allow for more reliable, stable, and scalable supply. FDA already evaluates manufacturing sites for these qualities and can help establish the criteria. In turn, manufacturers can be allowed to make limited claims in labeling attesting to upgrades that meet these criteria. These would include improvements in manufacturing that are believed to reduce the chance for error or lead to a process that can be more quickly scaled up in a time of shortage. Once producers that invested in these new processes get a green light to make certain claims on their labels that reflect these improvements, it would, in turn, trigger specific incentives – perhaps guaranteed purchase by government programs or preferential pricing under Medicare. This would provide a direct incentive for investing in the kind of manufacturing improvements that can help ensure a more scalable, and less trouble-prone supply of a product.

Conclusion

The problems fueling the recent shortages of sterile injectable drugs do not lend themselves to easy solutions because these episodes aren't typically driven by a single, common cause. Each shortage has unique features. In addition to the factors cited in this testimony, byzantine contracting arrangements, inefficient sourcing arrangements, a reluctance of hospitals to buy products 'off contract,'^{xix} problems with the sourcing of raw materials^{xx}, and a myriad of other factors all play a role in select shortage cases. There are, however, some flawed policy threads woven through all of these episodes. To the degree that some of these common issues stem from the way the price and manufacture of these drugs is regulated by government agencies, this presents policy makers obvious levers to start repairing this particular market. Before we start manipulating factors not in the control of government agencies, we should address factors that are in the direct purview of this committee.

I know one of the proposals before this committee is a system for early notification to FDA of impending shortages. I don't believe that relying on early notification of impending shortages is going to resolve these problems. In fact, I fear such a policy construct could make matters worse, by institutionalizing these shortages. Current proposals call for early notification from pharmaceutical companies when a factor arises that may result in a shortage. These factors may include changes made to raw material supplies, adjustments to manufacturer production capabilities and certain business decisions such as mergers, withdrawals or changes in output. In the end, the net effect of this legislation may simply be to provide an addition disincentive to firms who want to take one of these actions, even though these may be precisely the steps necessary to help ensure better long term supply.

The only way to improve the availability of these products is to make it profitable for firms to invest in the manufacturing that enables stable, safe, and more scalable supply. Policies enacted over the last few decades have systematically eroded the ability of manufacturers to earn returns on these products and make these investments. We need to reform the policies governing these markets if we're going to lure investment back into these important areas.

ⁱ Food and Drug Administration. Current drug shortages (<http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050792.htm>)

-
- ⁱⁱ Kaakeh R, Sweet BV, Reilly C, et al. Impact of drug shortages on U.S. health systems. *Am J Health Syst Pharm* 2011;68:1811-9.
- ⁱⁱⁱ UK Lawmakers to Probe Medicine Shortages. Reuters, November 21, 2011.
- ^{iv} Provisional observations on drug product shortages: Effects, causes, and potential solutions. Summary of a stakeholder's meeting on drug shortages convened by the American Medical Association and the American Society of Health-System Pharmacists. *American Journal of Health-System Pharmacists* 2002;59:173-182.
- ^v Kaakeh R, Sweet BV, Reilly C, Bush C, DeLoach S, Higgins B, Clark AM, Stevenson J. Impact of drug shortages on U.S. health systems. *American Journal of Health-System Pharmacy*. 2011;68:e13-e21.
http://www.ajhp.org/site/DrugShortages.pdf?fm_preview=1
- ^{vi} Mandy L. Gatesman and Thomas J. Smith. The Shortage of Essential Chemotherapy Drugs in the United States. *New England Journal of Medicine* 2011;365:18
- ^{vii} The report from ASPE states: "These gray market distributions appear to be a result of a drug shortage, not a cause, but the potential for hoarding and strategic behavior in the gray market is a concern with respect to future policy actions."
- ^{viii} According to the ASPE analysis, most of the production of a given drug is by three or fewer manufacturers in this space. Analysis of a sample of 33 generic sterile injectable oncology drugs shows that of 33 drugs, for 28 at least 90 percent of total unit sales in 2010 was by 3 or fewer manufacturers.
- ^{ix} The Health and Human Services Office of Assistant Secretary for Planning and Evaluation also found that supply and demand do not respond much to short-term changes in price. Rather than seeing a price increase when a disruption occurs, the drug instead goes into shortage. ASPE Issue Brief, "Economic Analysis of the Causes of Drug Shortages," October 2011.
- ^x Data presented by Steven Lynn, Chief, Recalls and Shortages, FDA/CDER Office of Compliance, Division of Manufacturing and Product Quality. Recalls, presentation to CASA, May 20, 2011, Baltimore, MD.
- ^{xi} FDA Faces Challenges Overseeing the Foreign Drug Manufacturing Supply Chain. Statement of Marcia Crosse Director, Health Care, GAO. September 14, 2011. Available at www.gao.gov/new.items/d11936t.pdf
- ^{xii} Corresponding to this increased regulatory scrutiny, the number of shortages has also increased almost proportionally. In 2005 and 2006 about 25 sterile injectable drugs were said to be in shortage by FDA. By 2009 that number had increased to about 75, matching the rise in the number of enforcement actions FDA took. By 2010 the number of parenteral drug shortages was put at more than 125 by FDA.
- ^{xiii} To Prevent Drug Shortages, Don't Look to Inspections, FDA Says. *The Pink Sheet Daily*, August 22, 2011
- ^{xiv} The ASPE report finds that problems in manufacturing are linked to 54% of shortages of sterile injectable drugs. The report finds that some of the largest manufacturers of sterile injectable drugs have had serious quality problems leading to temporary voluntary closure or renovations of major production facilities. This means that quality problems that affect an entire plant may result in shortages for many drugs.
- ^{xv} Congress has set the floor for FDA's Office of Generic Drugs funding at \$52.947 million in fiscal 2012, almost 5% less than the minimum of \$55.5 million it directed FDA to spend on OGD in fiscal 2011. FDA proposed a budget of \$88.8 million for OGD in fiscal 2012. But \$40 million of that was to have come from \$40 million in generic drug user fees that are not yet authorized.
- ^{xvi} Scott Gottlieb. Solving the growing drug shortages. *The Wall Street Journal*, November 07, 2011. A21 available at <http://www.aei.org/article/health/healthcare-reform/solving-the-growing-drug-shortages/>
- ^{xvii} ASPE Issue Brief, "Economic Analysis of the Causes of Drug Shortages," October 2011. For the 44 sterile injectable oncology drugs in shortage since 2008, these drugs experienced an average price decline of 26.5% between 2006 and 2008; 6.3% between 2008 and 2011; and 27.4% between 2006 and 2011. By contrast, the 28 generic injectable oncology products not in shortage since 2008 experienced small price increases over all these time periods.
- ^{xviii} Mandy L. Gatesman and Thomas J. Smith. The Shortage of Essential Chemotherapy Drugs in the United States. *New England Journal of Medicine* 2011;365:18
- ^{xix} Wynn Bailey. Globalization of the Life Sciences Supply Chain. *Contract Pharma*, January/February 2011. (available at www.contractpharma.com)
- ^{xx} More than 80% of the raw materials used in pharmaceuticals come from outside the United States.