Drug Shortages: Why they happen and what they mean

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

Chairman Baucus and Ranking Member Hatch: I want to thank you for the opportunity to testify today before the Senate Finance Committee about the shortages of some critical sterile injectable and infused drugs that doctors and patients are grappling with. My testimony today expands on comments I gave last week before the House Committee on Oversight and Government Reform on these same matters. Among other things, today I want to get into more detail on the genesis of some of these challenges, and in particular, the role that I believe pricing policies have played in impacting the markets for these drugs. I also want to provide the committee with my perspective on the impact that these shortages have had on patients and on the clinical practice of medicine. Finally, I will relate some new proposals for mitigating these challenges that I hope this committee will consider.

The problems have affected mostly older infused or “parenteral” drugs that are sold as generic medicines. Because these drugs have lost patent protection, they are typically sold at low prices and for slim profit margins. In fact, of the drugs that are in shortage, there is a clear correlation between price and availability – with many of the cheapest infused medicines also being the ones that seem most likely to be in shortage. These drugs are often sold for very low prices, sometimes just several dollars for a single dosage vial of a medicine. As a result, the cost of manufacturing ends up comprising a sizable proportion of the overall price of the finished medicine. In some cases, these drugs are being sold at a loss to their manufacturers once all the production and distribution expenses get fully loaded into the cost. The economic problems are widespread, and deeply embedded in the markets for these drugs. As a result, I fear the shortages will get worse before we see some relief.

Other countries are also experiencing drug shortages. Since many of the parenteral drugs manufactured for the U.S. are also sold in Canada, some of the same drugs in shortage here are also in shortage North of our border. Yet in the U.S. the critical medicines that are in scarce supply, and the protracted nature of the underlying causes of these shortages, make our situation uniquely challenging. In Europe, where generic medicines are often sold at higher prices, and where regulation of manufacturing has been more even in recent years, countries are facing few of the same shortage problems that we are seeing in the U.S.

I want to start today by reviewing the current problems, and providing the committee with some measure of the impact that these shortages are having on patient care. I will then review what I believe are some of the policy problems that have contributed to these current woes, and follow that with a description of what I believe are some potential solutions.

I should note up front, that I do not believe there is a discrete set of policy problems that have created these shortages. Nor do I believe there is a single collection of measures that can mitigate these circumstances. In fact, it is this absence of an identifiable set of primary causes that makes this problem so hard to resolve. Rather, the reasons for these shortages are multifactorial. Moreover, where policy failings have played a role, their impact has unfolded over many years and over successive political administrations. These elements are part of the reason why these problems are so protracted, and so hard for us to resolve.

Notwithstanding these complexities, I believe the best place for policymakers to begin addressing these challenges are with the common policy problems that are threaded, to
varying degrees, through many of these shortage episodes. They provide the most logical place for policymakers to start addressing the root causes of these drug shortages.

**Measure of the Problem**

Today, about 200 sterile injectable drugs are on the current shortage list kept by the American Society of Health-System Pharmacists. The vast majority of these shortage drugs (more than 80%) are generic medicines. Of the total market for generic sterile injectable drugs, fully 50% of these medicines are currently on the shortage list.

It has been said that the problems are being fueled by shortages of raw materials. Also, firms are said to be discontinuing manufacture of older generic drugs in favor of newer and more profitable ones. These elements, while at play in some of the individual drug shortages, tell only a small part of the story. The fact is that total generic manufacturing capacity has increased in recent years (from 54 million unites to 56 million units over the last five years).

The more revealing market phenomenon is the growing concentration of manufacturing in a smaller number of increasingly large suppliers. This consolidation creates a lot of operational efficiency. That enables these low-margin products to be produced at their low price points. But it also creates some additional risks. It means that when any single manufacturer experiences a disruption in their production, a significant shortfall can ensue across a whole multitude of different drugs. It should therefore be no surprise that only one or a few companies manufacture many of the drugs on the shortage list. Of the 168 products that IMS Health lists on its shortage list, seven currently have no suppliers, while 56 products have one supplier, and another 23 have two suppliers. Moreover, the manufacturing of most of these generic sterile injectable drugs is concentrated about six very large suppliers.

Oncology drugs make up the highest share of the drugs in shortage, fully 16%. This impacts nearly 550,000 patients annually, comprising 28 different generic injectable cancer products. Shortages of drugs have triggered clinical mistakes and bad outcomes in situations where patients received medicines that prescribers weren’t accustomed to using. The medical literature is replete with case reports of critical, life-saving drugs that have been in shortage, where doctors were forced to adopt suboptimal alternatives. For example:

Since autumn 2009 the anesthetic drug propofol has been facing production issues. Some institutions lacking propofol have used midazolam or dexmedetomidine instead. Both agents are similar to propofol but do not precisely mirror the quick time to onset and offset or level of sedation provided by propofol. In each case, there are reports of patients becoming dangerously over sedated because hospital staff was unfamiliar with using the new agents.

In the case of propofol, the FDA allowed another version of the drug to be imported temporarily. However, this alternative medication does not contain an antimicrobial retardant. As such, strict aseptic technique had to be used in administering this version of the drug --- techniques clinicians weren’t accustomed to requiring with the drug.

Severe shortages of leucovorin, used to treat colorectal cancer, prompted the American Society of Clinical Oncology (ASCO) to issue a clinical alert in 2009. ASCO suggested substitution of leucovorin with levolofolate, which is much more expensive and is only
approved by the FDA for use as a rescue drug after administration of high-dose methotrexate in patients with osteosarcoma. Levofofolinate in combination with irinotecan and fluorouracil seems effective in patients with metastatic colorectal cancer, but it is unclear whether addition of this agent to other chemotherapy regimens would replicate the responses expected of leucovorin; thus there is a risk attached to this strategy.\textsuperscript{xiv}

I have seen some of these problems first hand. I practice hospital-based medicine. When a drug is declared to be in shortage, there is pressure put on doctors to find alternative therapies, in order to conserve the shortage drugs for the most urgent cases. I have never seen a situation in my own clinical work where doctors couldn’t find an adequate alternative drug to substitute for a medicine that was not available. But I can tell you that I have seen the process of grappling with these issues cause problematic delays in administering critical care. Many hospitals are being forced to ration key medicines and patients to sit on waiting lists for vital drugs.\textsuperscript{xv} For all of these reasons, the drug shortages are also costing a lot of money, adding to an already overburdened healthcare system. The costs associated with managing shortages in the United States are an estimated to total $216 million annually.\textsuperscript{xvi xvi}

Finding Solutions

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 causes of these shortages are often multifactor and stem from many conditions outside of the easy grasp of policymakers. I would urge this committee to focus its attention on those elements that are in its direct purview and that re-appear as common factors that are woven through many of these shortage episodes. To these ends, there are things we can do immediately to help mitigate some of the pressure on the market for these drugs. There are steps we need to take that may not have an immediate impact, but will start to repair these markets for the long run. I group these elements into three categories:

The first are mechanisms that make prices sticky, limiting profitability and precluding investment in new supply and more efficient manufacturing.\textsuperscript{xviii} The policies that make prices inflexible also prevent firms from taking price increases as their cost of goods rise.

The second are regulatory challenges that have made production of these drugs safer and more reliable, but also in some cases substantially increased the cost of goods at the very time that policies have made it hard for producers to take and sustain price increases.

The third category is market structures that prevent firms from being able to earn appropriate returns when they invest in key improvements in manufacturing that creates production that is more reliable and can be more easily scaled to meet changes in demand.

Regulation of Drug Pricing

The most significant issue in these markets is that pricing is sticky. When demand for these drugs increases, or more importantly, when the cost of developing these medicines rises, manufacturers can’t take and sustain price increases to make up for these market changes.
This makes it hard for manufacturers to make the long-term (2-7 year) investments needed to stand up new facilities or upgrade existing facilities to produce more supply.

A search for the origin of that sticky pricing has to begin with the way Medicare reimburses these products. 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 because the average is computed off six months of backward looking prices. 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 about six months later. As a result, the purchasers of a drug (in this case, mostly hospital outpatient clinics and 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 lower “average sales price” that Medicare reimburses for the medicine.

This makes it hard for manufacturers to take, and sustain price increases to reflect demand or -- more importantly -- their rising cost of producing these goods. For one thing, even if a single manufacturer raises its price, this price increase will be diluted once it gets averaged into the prices charged by competitors. Unless manufacturers were to illegally collude to raise their prices simultaneously, the average sales price will always be pushed lower by the impact of the lowest cost product. This might be a firm who can produce drugs at lower costs only owing to uneven regulation of manufacturing facilities that raises costs for only a handful of firms at a time. Or it might be firms who are willing to take losses on particular generic drugs in order to win more lucrative contracts on other medicines. Once the ASP gets driven down by a single producer, who might get into the market for only a very short time, it is very hard for the ASP to ever rise again after it has been pushed to the floor.

Moreover, many of the manufacturers producing these parenteral generic drugs do so in order to win group purchasing contracts with large institutions. They often view these drugs as “loss leaders” that allow them to get contracts that enable them to sell more profitable medicines. For this reason, they’re reluctant to raise prices to match rising production costs if it means putting at risk much larger contracts covering dozens if not hundreds of other products. But that also means they will be reluctant to invest in improved manufacturing capacity. When faced with rising production costs, the easier path for some manufacturers is to cease production of a drug entirely rather than raise prices and disrupt contracts.xix

In order to make the long-term, capital intensive investments needed to bring on new manufacturing capacity, 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 the 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 never in shortage over this period, in most cases, rose.** Moreover, any examination of the list of shortage drugs will show that the lowest-priced drugs are also the ones most often in shortage.

The bigger issue with the way Medicare reimburses these drugs, however, is the way it sets a single, flat price for each 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 (computed off the average sales price) that it will pay for
each code, and in turn, each drug category. This means that the price reflects the blended average of all the drugs in a particular category, regardless of which manufacturer is producing the drug. So even if a drug has multiple manufacturers, some better or higher-cost producers than others, all of the drugs in a particular category will be paid the same rate.

Since FDA’s enforcement of facilities is often uneven, at any given time one particular manufacturer might be facing more scrutiny, and in turn higher production costs, relative to its competitors. By lumping all of the drugs into the same billing code, the price paid ends up reflecting the terms of the lowest cost producer. This situation creates pressure to shave down manufacturing costs. Once ASP falls to a new, lower level, it is hard for it to rise again because of its stickiness. So firms end up in a race to the bottom on manufacturing costs.

This race to the bottom on manufacturing can work reasonably well in producing significant savings when it comes to products that are easy and cheap to manufacture, like small molecule drugs (pill forms). 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 investments are forgone. The end result is that there is little margin left over for investing in expanding or improving manufacturing facilities.

**Regulation of Drug Manufacturing**

The regulation of pricing is made more problematic by the fact that production costs have been increasing owing to more stringent regulation of manufacturing. In recent years, the Food and Drug Administration (FDA) has gotten tougher on potentially dangerous problems that have long plagued the production of some injectable generic drugs. These include problems with sterility, and particulate matter getting into the solutions.

The FDA has real concerns about the integrity of how some of these drugs are manufactured. For example, contribution to the finished solution from equipment, process, components, and packaging should never be considered acceptable. 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 some less well-capitalized manufacturers; that increased regulation has caught them off guard. Low margin producers can’t easily meet new regulatory mandates.

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. With its vigilance heightened, the FDA has required manufacturers to undergo major plant renovations, suspend facilities or stop shipping goods from suspect production lines. 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 reported drug shortages.

The increased FDA scrutiny doesn’t just apply to the finished forms of these drugs, but in particular, to the ingredients in these medicines – the Active Pharmaceutical Ingredients or API. After the safety issues related to Heparin several years ago, FDA dramatically stepped up its oversight of API suppliers, especially ingredients coming from foreign sources.
There are other factors that have contributed to a sharp and rapid increase in the cost of goods of many of drugs. For example, precious metals such as platinum are a component of some drugs. It’s clear what have happened to commodity prices in recent years. But changing regulatory standards are the most significant driver of rising cost of goods in this space. If we want to maintain high standards, we need policy measures that 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. When it comes to injectable drugs, this starts with the process for remediating facilities recently taken off line as a result of regulatory action. FDA must prioritize getting these facilities producing as quickly as possible after necessary renovations are made.

To these ends, an issue at play in these shortages relates 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. It seems almost inevitable that some of these backlogged manufacturing supplements sat in this backlog while the drug approached the precipice of the shortage list.

The backlog in reviewing manufacturing supplements can add as much as a several year delay to approval of those manufacturing changes. These supplements are usually 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. To these ends, the Generic Drug User Fee program should provide FDA with money to tackle this backlog.225 Congress should build into this legislation specific measures to 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.

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 move away from the flawed “average sales price” when it comes to reimbursing the generic sterile injectable drugs and pay for these drugs according to a more
flexible, market based price that could more easily adjust to market conditions. One consideration is to reimburse these drugs based on the price paid by wholesalers on the open market. This wholesale acquisition cost (WAC) is already collected and reported to Medicare. Reimburse the parenteral drugs according to WAC would allow generic firms to adjust charges to match rising production costs and demand. Congress might also consider allowing ASP to be “re-set” in some fashion for drugs that are approaching the zone of shortage, or are considered critical and prone to shortage by some authoritative group such as USP, FDA, or the Society of Health System Pharmacists. This re-setting of ASP could be to a more market-based price – either WAC (which has its own flaws) or some new “spot” price that Medicare requires reporting on that is more forward looking.

These drugs should also be exempt from Medicaid price-control schemes that serve to distort market prices and reduce profitability and incentives to invest in new production. These include Medicaid Best Price rules and the 340B drug discount program. With respect to 340B, perhaps the most damaging proposal would be to expand this program to the hospital inpatient side. Such a proposal could have a significant impact on profits on these drugs, and could dramatically impact decisions to invest in new lines or expanded facilities.

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 manufacturers 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.

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 didn’t alter the clinical properties of a drug. FDA could be directed to establish criteria for which manufacturing improvements are believed to allow for more reliable, stable, and scalable supply. In turn, manufacturers can be permitted to make limited claims in labeling attesting to upgrades that meet these manufacturing criteria.

A significant factor in recent shortages is the lack of excess capacity in the market owing to economic factors (the profit margins on these drugs are so slim it doesn’t make economic sense to keep excess manufacturing capacity on hand). The manufacturing capacity that exists is not scalable, meaning that production cannot be easily ramped up at one manufacturing site to make up for shortfalls should another production site experience problems. If only a few companies make a drug and one of them encounters a manufacturing problem, the remaining competitors may not be able to meet the demand.

To address these challenges, once producers invested new processes and are approved to make certain claims on their labels that reflect improvements in manufacturing to make the process more reliable, these claims could then trigger specific incentives – perhaps guaranteed purchase by government programs or preferential pricing under Medicare (for example, through a pass through payment under the DRG). 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 supple of a product.

We need to view production capacity for critical drugs as a national strategic asset. In the past, government approached similar issues by coming up with targeted incentives (such as tax credits) to encourage development of more domestic manufacturing capacity. This was the approach taken to enabling more domestic capacity for production of flu vaccine. That episode provides some good proxies for how we might resolve the current shortages.

Having more investment in domestic manufacturing will also help stimulate creation of skilled domestic jobs. Right now, there are very few companies investing in new domestic facilities because of the economic advantage of taking these activities overseas.

When a system of competitive bidding drove down the price of flu vaccine to a level that made investment in expanded and improved manufacturing unviable, some severe shortages arose when outdated manufacturing facilities experienced regulatory problems. The situation was resolved with policies that, among other things, created incentives for development of new, domestic manufacturing capacity; and regulatory approaches that made evaluation and approval of new manufacturing sites and brands of vaccines more efficient. xxvii

In the market for generic injectable drugs, a large part of the reason why adequate incentives don’t already exist for investment in new production capacity relates to the inability of manufacturers to take and sustain price increases to offset the cost of these investments. So first and foremost, we need to fix these pricing policies. Many stem from the way Medicare treats these products. But we shouldn’t expect these solutions to have an immediate payoff.

In the short run, there may be little we can to stimulate investments in new production capacity that will translate into immediate supply increases. The bottom line is we need to address policy reforms that will enable us to have more stable supply in the future, but it will take time (in some cases years) to stand up these new facilities. To resolve these shortages in the short term, we should focus equal attention on the existing manufacturing capacity that is available, but has been taken offline as a result of regulatory findings. A significant amount of manufacturing capacity is currently undergoing remediation owing to concerns raised by the FDA. The most immediate impact we can have on these shortages is to make sure the process for getting this manufacturing capacity remediated, and bringing it into regulatory compliance, is as efficient as possible. We should focus some attention on the resources that would enable FDA to help producers get these renovated facilities quickly back on line.

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 (where large GPOs lock in prices for a few years at a time, and put caps that prevent manufacturers from taking price increases), inefficient sourcing arrangements, a reluctance of hospitals to buy products ‘off contract,’ xxviii problems with the sourcing of raw materials, xxix and a myriad of other factors all play a factor.
There are, however, some flawed policy threads woven through 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 market. Before we start manipulating factors not in the control of government agencies, we should address factors that 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 additional 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. Companies will be reluctant to take business decisions that invite FDA inspectors to pick through their facilities and operations, even if these decisions might shore up shortage drugs.

If the Senate does grant FDA with this new authority, I would urge members to monitor its implementation closely. To the degree that FDA would get information from manufacturers that could help to predict shortages, we should audit this process. If shortages continue to occur, we should understand why these were allowed to take place in situations where FDA had warning of the impending problem. In some cases, there will have been regulatory steps that could have been taken to mitigate a future shortage. We should understand whether the consequences of the shortage itself were less significant than the consequences of whatever regulatory steps might have prevented the shortage situation (such as allowing a facility with deficiencies to nonetheless continue to produce and ship drug under closer supervision).

Congress should also take steps to make sure FDA’s internal communication around these issues is efficient and properly resourced as well. I was told of at least one situation where a major manufacturing facility was voluntarily shut down and created a shortage of some critical drugs, but FDA’s drug shortage office was not aware of the situation until after the fact even though FDA’s field inspectors knew about the pending action for some time.

Some also blame these shortages on what they refer to as “manipulation” of drug middlemen or so-called “gray market” distributors. However unpleasant, the markups charged by small distributors often reflect their higher costs, and aren’t simply profiteering as has been alleged. In select cases where middle market distributors are using the existence of a shortage to earn windfall profits, and can be legitimately said to be taking advantage of these situations, the activity – however unsavory – is also not a cause of the shortage, but a sad symptom of the larger problems. We need to make sure that in our effort to come up with proactive measures to address these shortages, we don’t end up making them worse. Cracking down on inappropriate profiteering, while an important endeavor, won’t solve the shortages and will only add to our challenges if it ends up also impacting the legitimate activity of small distributors that help plug gaps in the existing supply chain. Legislation to address the “gray market” needs to make clear distinctions between legitimate and illegitimate activity, and it may be hard in some cases to distinguish this on price alone.
Many small distributors routinely provide critical-need products to hospitals that cannot otherwise secure these same products from their primary wholesalers. This is especially important in rural areas. Moreover, small and independent distributors typically must purchase products at prices above the Wholesale Acquisition Costs. They cannot access drugs at the lower prices that GPOs negotiate with manufacturers. As a result, the difference between the higher prices charged by small distributors and those typically provided to hospitals by GPOs can often be misleading. What might appear as an enormously priced drug being offered by a small distributor may actually reflect an appropriate mark-up.

Like the “gray market,” the lack of qualified manufacturers for these drugs is also not a cause for the shortages. Here again, the lack of qualified manufacturers is another symptom of the underlying problems. True, the absence of multiple manufacturers makes shortages for any particular drug more likely to occur. But 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. The existence of shortages in the market for sterile injectable drugs has more to do with the lack of pricing power in this market, and the under-investment in manufacturing in an enterprise where the margin for error is narrow, and driving down cost of goods creates its own risks.

Policy makers have also 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.

The only way to improve the availability of these products is to make it possible for firms to keep pace with rising production costs and earn enough returns to invest back in better manufacturing that enables stable, safe, and more scalable supply. Policies enacted over the last few decades have systematically eroded the ability of manufacturers to price these products in ways that keep up with rising costs. Instead, this market has been challenged by a race to the bottom on manufacturing costs. This isn’t a healthy dynamic in markets where production is not a trivial affair and where increasing regulatory requirements demand new investments in manufacturing facilities. We need to reform the policies governing how these products are priced if we’re going to attract new investment into these important areas.
This testimony is based on written testimony delivered before a hearing of the House Committee on Oversight and Government Reform, Healthcare Subcommittee on November 30, 2011. Dr. Gottlieb consults with and invests in healthcare companies.

1 UK Lawmakers to Probe Medicine Shortages. Reuters, November 21, 2011.
3 The Canadian Pharmacists Association surveyed members in October 2010 about whether they were unable to fill any prescriptions during their most recent shifts, and over the previous week. Of the more than 600 pharmacists who responded online, 84% had problems locating a drug during their most recent shift, and 94% could not find at least one drug in the previous week.
4 Food and Drug Administration. Current drug shortages (http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050792.htm)
7 Drug Shortages: A closer look at products, suppliers, and volume volatility. IMS Institute for Healthcare Informatics, November 2011.
8 Drug Shortages: A closer look at products, suppliers, and volume volatility. IMS Institute for Healthcare Informatics, November 2011.
15 The Lancet Oncol. Editorial. April 2011;4:313
19 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.
21 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.
22 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.
23 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.
24 To Prevent Drug Shortages, Don’t Look to Inspections, FDA Says. The Pink Sheet Daily, August 22, 2011
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.

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.


More than 80% of the raw materials used in pharmaceuticals come from outside the United States.

Preserving Access to Life-Saving Medications Act (S.296)


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.”

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 20010 was by 3 or fewer manufacturers.
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FDA acts to bolster supply of critically needed cancer drugs

Announcements build on President Obama’s Executive Order

The U.S. Food and Drug Administration today announced a series of steps to increase the supply of critically needed cancer drugs and build on President Obama’s Executive Order to help prevent future drug shortages.

“A drug shortage can be a frightening prospect for patients and President Obama made it clear that preventing these shortages from happening is a top priority of his administration,” said FDA Commissioner Margaret A. Hamburg, M.D. “Through the collaborative work of FDA, industry, and other stakeholders, patients and families waiting for these products or anxious about their availability should now be able to get the medication they need.”

In response to the critical shortage of the cancer drug Doxil (doxorubicin hydrochloride liposome injection) and rapidly declining supplies of methotrexate, the FDA took proactive steps needed to increase available supply for patients in the U.S. For Doxil, there will be temporary importation of a replacement drug, Lipodox (doxorubicin hydrochloride liposome injection), which is expected to end the shortage and fully meet patient needs in the coming weeks. For methotrexate, in addition to already announced actions, the Agency has approved a new manufacturer of preservative-free formulation of methotrexate that is expected to further bolster supply and help avert a shortage of this lifesaving medicine. FDA expedited review of the application to help address this potential shortage.

In addition, in response to President Obama’s Executive Order on prescription drug shortages, FDA today issued draft guidance to industry on detailed requirements for both mandatory and voluntary notifications to the agency of issues that could result in a drug shortage or supply disruption. Increased awareness of the importance of early notification due to President Obama’s Oct. 31, 2011, Executive Order and FDA’s letter to manufacturers on the same day has resulted in a sixfold increase in voluntary notifications by industry of potential shortages. In 2011, there were a total of 195 drug shortages prevented. Since the Executive Order, FDA has prevented 114 drug shortages.

With regard to methotrexate, a drug that is needed for the treatment of many forms of cancer and other serious diseases, FDA has successfully engaged many firms to assist in maintaining supplies to meet all patient needs. Preservative-free methotrexate is needed for the intrathecal (injection into the fluid surrounding the brain and spinal cord) treatment of children with acute lymphocytic leukemia (ALL) and for the high-dose therapy of osteosarcoma.

First, FDA has prioritized review of and approved a preservative-free methotrexate generic drug manufactured by APP Pharmaceuticals and expects that product to become available in March and continue indefinitely. Second, Hospira expedited release of additional supplies, resulting in 31,000 vials of new product – enough for more than one month’s worth of demand – being shipped to hundreds of U.S. hospitals and treatment centers today. FDA is actively working with other manufacturers of methotrexate who have also stepped up to increase production in order to meet patient needs, including Mylan and Sandoz Pharmaceuticals.

APP’s application for preservative-free methotrexate is a supplement to its already approved generic drug application that the firm had previously discontinued. When FDA became aware of potential problems with the supply of the drug (due to the largest manufacturer, Bedford/Ben Venue voluntarily closing its plant), the Agency reached out to other firms to see how FDA could assist to meet the shortfall.

Get these high resolution captioned photos of the FDA Drug Shortages Briefing on Flickr.

Watch this interview with Sara Stuckey, a mother of a young cancer patient with first-hand drug shortage experience. For more interviews go to the FDA Drug Shortage playlist on YouTube.

High quality video is available for credentialed media. Contact Shelly Burgess at Shelly.Burgess@fda.hhs.gov.
Prior to approval of APP's application and subsequent to Ben Venue's voluntary shutdown, FDA worked with Ben Venue on release of already manufactured preservative-free methotrexate, following confirmation of its safety. This supply is available already and will provide emergency supplies as the other firms also work to increase production of methotrexate in response to requests by FDA and the public.

The Administration also announced on October 31, 2011, its support for bipartisan legislation that would require all prescription drug shortages to be reported to FDA and would give FDA new authority to enforce these requirements. While additional manufacturing capacity is necessary to fully address the drug shortage problem, additional early notification to FDA can have a significant, positive impact on addressing the incidence and duration of drug shortages.

For more information:
- Drug Shortages
- Drug Shortage Guidance
- Labeling for Doxil (doxorubicin hydrochloride liposome injection)
- February 21, 2012, Letter to Healthcare professionals regarding doxorubicin
- Labeling for methotrexate

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency is also responsible for the safety and security of our nation’s food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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Press Announcements > FDA acts to bolster supply of critically needed cancer drugs

Links on this page:

1. http://www.youtube.com/playlist?list=PLCEF0EB78DFE07E4E
By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

**Section 1. Policy.** Shortages of pharmaceutical drugs pose a serious and growing threat to public health. While a very small number of drugs in the United States experience a shortage in any given year, the number of prescription drug shortages in the United States nearly tripled between 2005 and 2010, and shortages are becoming more severe as well as more frequent. The affected medicines include cancer treatments, anesthesia drugs, and other drugs that are critical to the treatment and prevention of serious diseases and life threatening conditions.

For example, over approximately the last 5 years, data indicates that the use of sterile injectable cancer treatments has increased by about 20 percent, without a corresponding increase in production capacity. While manufacturers are currently in the process of expanding capacity, it may be several years before production capacity has been significantly increased. Interruptions in the supplies of these drugs endanger patient safety and burden doctors, hospitals, pharmacists, and patients. They also increase health care costs, particularly because some participants in the market may use shortages as opportunities to hoard scarce drugs or charge exorbitant prices.

The Food and Drug Administration (FDA) in the Department of Health and Human Services has been working diligently to address this problem through its existing regulatory framework. While the root problems and many of their solutions are outside of the FDA’s control, the agency has worked cooperatively with manufacturers to prevent or mitigate shortages by expediting review of certain regulatory submissions and adopting a flexible approach to drug manufacturing and importation regulations where appropriate. As a result, the FDA prevented 137 drug shortages in 2010 and 2011. Despite these successes, however, the problem of drug shortages has continued to grow.

Many different factors contribute to drug shortages, and solving this critical public health problem will require a multifaceted approach. An important factor in many of the recent shortages appears to be an increase in demand that exceeds current manufacturing capacity. While manufacturers are in the process of expanding capacity, one important step is ensuring that the FDA and the public receive adequate advance notice of shortages whenever possible. The FDA cannot begin to work with manufacturers or use the other tools at its disposal until it knows there is a potential problem. Similarly, early disclosure of a shortage can help hospitals, doctors, and patients make alternative arrangements before a shortage becomes a crisis. However, drug manufacturers have not consistently provided the FDA with adequate notice of potential shortages.

As part of my Administration’s broader effort to work with manufacturers, health care providers, and other stakeholders to prevent drug shortages, this order directs the FDA to take steps that will help to prevent and reduce current and future disruptions in the supply of lifesaving medicines.

**Sec. 2. Broader Reporting of Manufacturing Discontinuances.** To the extent permitted by law, the FDA shall use all appropriate administrative tools, including its authority to interpret and administer the reporting requirements in 21 U.S.C. 356c, to require drug manufacturers to provide adequate advance notice of manufacturing discontinuances that could lead to shortages of drugs that are life supporting or life sustaining, or that prevent debilitating disease.

**Sec. 3. Expedited Regulatory Review.** To the extent practicable, and consistent with its statutory responsibility to ensure the safety and effectiveness of the drug supply, the FDA shall take steps to expand its current efforts to expedite its regulatory reviews, including reviews of new drug suppliers, manufacturing sites, and manufacturing changes, whenever it determines that expedited review would help to avoid or mitigate existing or potential drug shortages. In prioritizing and allocating its limited resources, the FDA should consider both the severity of the shortage and the importance of the affected drug to public health.

**Sec. 4. Review of Certain Behaviors by Market Participants.** The FDA shall communicate to the Department of Justice (DOJ) any findings that shortages have led market participants to stockpile the affected drugs or sell them at...
exorbitant prices. The DOJ shall then determine whether these activities are consistent with applicable law. Based on its determination, DOJ, in coordination with other State and Federal regulatory agencies as appropriate, should undertake whatever enforcement actions, if any, it deems appropriate.

Sec. 5. General Provisions. (a) Nothing in this order shall be construed to impair or otherwise affect:

(i) authority granted by law to an agency, or the head thereof; or

(ii) functions of the Director of the Office of Management and Budget relating to budgetary, administrative, or legislative proposals.

(b) This order shall be implemented consistent with applicable law and subject to the availability of appropriations.

(c) This order is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity by any party against the United States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.

BARACK OBAMA

THE WHITE HOUSE,
October 31, 2011.
Fact Sheet: Obama Administration Takes Action to Reduce Prescription Drug Shortages in the U.S.

While the Food and Drug Administration has successfully prevented 137 drug shortages since the beginning of 2010, drug shortages have been increasing in frequency and severity in recent years and adversely affecting patient care. A small number of drugs in the U.S. experience a shortage in any given year, but the number of reported prescription drug shortages in the United States nearly tripled between 2005 and 2010, going from 61 to 176. There are many causes and potential solutions to this challenge and addressing this significant public health problem will require the urgent attention of industry, other stakeholders, and government.

Today, President Obama will issue an Executive Order directing the FDA and Department of Justice to take action to help further reduce and prevent drug shortages, protect consumers, and prevent price gouging. These additional steps for early notification will help achieve some of the goals of bipartisan legislation in Congress, which the President supports, that will strengthen the FDA’s ability to prevent prescription drug shortages in the future.

The Executive Order is one in a series of steps that will help address the shortage of prescription drugs and ensure patients have access to the lifesaving medicines they need. Today, the Obama Administration will also:

• Send a letter to drug manufacturers reminding them of their legal responsibility to report the discontinuation of certain drugs to the FDA. The letter also encourages companies to voluntarily notify FDA about potential prescription drug shortages in cases where notification is not currently required.
• Increase staffing resources for the FDA’s Drug Shortages Program to address the increased workload that will result from additional early notification of potential shortages by manufacturers.
• Release a report from the Department of Health and Human Services Office of the Assistant Secretary for Planning and Evaluation (ASPE) that assesses the underlying factors that lead to drug shortages, and an FDA report on its role in monitoring, preventing, and responding to these shortages.

President Obama’s Executive Order
Early notification of potential drug shortages can help FDA work with drug manufacturers, hospitals, doctors, and patients to prevent or mitigate a shortage before it becomes a crisis. Currently, Federal law requires drug manufacturers to notify FDA when production of critical drugs provided by only one manufacturer is being discontinued. The President’s order directs FDA to broaden reporting of potential shortages of certain prescription drugs. Additionally, the Executive Order requires FDA to expand its current efforts to expedite review of new manufacturing sites, drug suppliers, and manufacturing changes to help prevent shortages.

While additional manufacturing capacity is necessary to fully address the drug shortage problem, early disclosure can have a significant, positive impact on the incidence and duration of drug shortages. This year alone, voluntary early notification by manufacturers allowed FDA to successfully prevent 99 drug shortages. Once FDA is notified of an existing shortage, the agency has multiple options to prevent or mitigate the drug shortage, and in many cases, takes more than one action. In the shortages studied, the agency’s three most common actions were:

• Asking other firms to increase production (31%),
• Working with manufacturers to identify ways to mitigate quality issues, i.e. flexibility through regulatory discretion (28%), and
• Expediting review of regulatory submissions (26%).

FDA has also exercised regulatory discretion regarding controlled importation of similar products approved abroad but not approved in the United States in 5 percent of cases.

Fighting Price Gouging
The President’s Executive Order also directs FDA to work with the Department of Justice to examine whether any secondary drug wholesalers or other market participants have responded to potential drug shortages by illegally hoarding medications or raising prices to gouge consumers. For example, the ranking member of the House Committee on Oversight and Government Reforms, when announcing his investigation into so-called gray markets, expressed concerns about a report that a leukemia drug whose typical contract price is about $12 per vial was being sold at $990 per vial – 80 times higher. A Premier healthcare alliance report released in August estimated that the typical gray market vendor marks up prices by an averaged 650 percent. At the extreme, a drug used to treat high blood pressure that was normally priced at $25.90 was being sold at $1,200 due to a shortage.
Pending Legislation
These additional steps for early notification will help achieve some of the goals of bipartisan legislation sponsored by Senator Amy Klobuchar (S. 296) and Congresswoman Diana DeGette (D-CO) (H.R. 2245). Backed by the President, this legislation would require all prescription drug shortages to be disclosed and give the Food and Drug Administration additional authorities to enforce these requirements. In the meantime, to complement the broadened notification and consistent with the goals of this legislation, the FDA will establish a voluntary notification process that will encourage manufacturers to disclose more potential shortages.

Increased Staffing Resources for the FDA Drug Shortages Program
Over the coming weeks, the FDA will tap six to eight members of a surge team with critical skills from across the Department to work in the Drug Shortage Program to enhance the Agency’s ability to prevent and mitigate drug shortages as a result of increased early notification by manufacturers. When FDA becomes aware of a potential drug shortage, this Program works collaboratively with the affected firms to return the product to its usual market availability as quickly and as safely as possible while helping prevent any harm to patients. It also encourages other firms that make the drug to ramp up production if they are willing to do so, expedites the review of submissions from manufacturers which may include requests to extend the expiration date of products, increase capacity, use a new raw material source, license new manufacturers, and permit changes in product specifications. And, for manufacturing and quality problems, FDA works with the firm to address the issues.

New Analyses from the Department of Health and Human Services
The HHS Assistant Secretary for Planning and Evaluation conducted an assessment of the underlying economic factors that lead to prescription drug shortages, particularly market factors that have contributed to shortages of sterile injectable oncology drugs. The report finds that over the last several years, growth in demand has occurred while the capacity of manufacturing facilities has remained stable, unable to keep up with demand. Although sterile injectable drugs are a small percentage of the overall prescription drug market, they make up a disproportionate share of drugs in shortage and include critical drugs, such as oncology drugs. Their report concludes that over time, entry of additional manufacturing facilities, and expansions in capacity should reduce the frequency of shortages due to supply disruptions. The Administration plans on further outreach the industry, oncologists, and people with cancer to identify additional ideas on actions.

In addition, to better understand drug shortages, the FDA conducted a review of medical product shortage activities in its four medical product Centers, with an emphasis on reviewing what the agency has already done and is currently doing to address drug shortages. FDA also spoke with external stakeholders to understand their perspectives on the current drug shortage problem. Based on these conversations, a review of published and unpublished information on drug shortages, and analyses of databases either available or created for the report, the reports find that the shortage problem is complex and stems from economic, legal, regulatory, policy, and clinical decisions that are deeply interconnected. FDA continues to work with manufacturers to help prevent and mitigate these shortages, but many potential solutions to drug shortages will require collaborative efforts among all relevant stakeholders.

Key Facts about Drug Shortages

- The number of reported drug shortages annually has tripled from 61 in 2005 to 178 in 2010.
- Of the 127 studied shortages in 2010-11, 80 percent involved drugs delivered to patients by sterile injection, including oncology drugs, antibiotics, and electrolyte/nutrition drugs.
- The leading reasons for the reported shortages were problems at the manufacturing facility (43%), delays in manufacturing or shipping (15%), and active pharmaceutical ingredient shortages (10%).
- Manufacturing quality problems that have resulted in shortages can be serious, including findings of glass shards, metal filings, and fungal or other contamination in products meant for injection into patients.
- Sterile injectable drugs have unique manufacturing and market features which make shortages of these products more likely to occur and harder to prevent or mitigate, including:
  - Manufacturing them is complex and can more easily lead to problems that affect safety,
  - Dedicated manufacturing lines are often required,
  - The top three generic injectable manufacturers hold 71% of the market by volume,
  - Most sterile injectables have one manufacturer that produces at least 90% of the drug, and
  - “Just in time” manufacturing and inventorying practices leave little margin for error.
Guidance for Industry

Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Kalah Auchincloss at 301-796-0659 or (CBER) Stephen Ripley at 301-827–6210.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2012
Procedural
Guidance for Industry

Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage

DRAFT GUIDANCE

Additional copies are available on the Internet at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm and from these FDA Offices and Centers:

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Guidance for Industry

Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage

This guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s or Agency’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document provides guidance to industry on requirements for notification to FDA of a discontinuance of certain drug products under section 506C of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as implemented by 21 C.F.R. §§ 314.81(b)(3)(iii) and 314.91. The guidance reflects amendments to the implementing regulations published as an interim final rule on December 19, 2011 (effective January 18, 2012). This document also provides guidance to industry on voluntary notification to FDA of issues that may result in a shortage or potential disruption in supply of a prescription drug or biological product in the U.S. market, regardless of whether mandatory notification is required under section 506C. This guidance is intended for manufacturers of prescription drug and biological products regulated by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER).

Under section 506C of the FD&C Act, “sole manufacturers” are required to report to FDA discontinuances of drug products that are “life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition.” On October 31, 2011, FDA sent a letter to manufacturers of prescription products reminding them of their mandatory reporting requirements under section 506C and encouraging them to voluntarily report to the Agency any disruptions in supply that could lead to a product shortage, even beyond those situations covered in this guidance.

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1 This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.
2 Interim Final Rule, Applications for Food and Drug Administration Approval To Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance, 76 FR 78530 (December 19, 2011).
3 Section 506C only applies to drugs that are approved under section 505(b) or (j) of the FD&C Act. Section 506C does not apply to drugs that are biological products licensed through a biologics license application (BLA) under section 351 of the Public Health Service Act. However, drugs that are biological products are also vulnerable to shortages and are addressed in the voluntary notifications sections of this guidance. “Biological products” in this guidance refer to biological drug products.
by mandatory reporting. On the same day, the President issued Executive Order 13588 directing FDA to use all available administrative tools to expand the Agency’s efforts to combat the problem of drug shortages.

This document is intended to provide additional guidance to industry on the existing mandatory reporting requirements under section 506C, as well as additional explanation of the voluntary notification process. For both mandatory and voluntary notifications, this guidance explains why FDA should be notified, who should notify the Agency, what information should be reported, when and how to notify the Agency, and what FDA will do with reported information. The guidance also discusses certain advance planning strategies that manufacturers can consider to prevent or mitigate product shortages.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Public Health Impact of Drug Shortages: Why Notification to the FDA of Issues that May Lead to a Drug Shortage is Critical

FDA is concerned about the rising incidence of drug shortages in the United States, particularly those involving drugs that are manufactured by a small number of firms and for which there are no good therapeutic substitutes available. While not all drugs experience shortages, the number of drug shortages has been rising steadily over the last five years, nearly tripling from 61 in 2005 to 178 in 2010. In 2011, FDA tracked over 250 drug shortages. Drug shortages can create significant public health concerns. For example, some drug shortages delay or deny needed care for patients, because they involve drugs used to treat cancer, to fight infectious diseases, to provide required nutrition, or to address other serious medical conditions. Other shortages force providers to prescribe second-line alternatives, which can be less effective and higher risk than first-line therapies. In a survey by the Institute for Safe Medication Practices of 1,800 healthcare practitioners, a majority reported problems with drug shortages, including the use of less desirable, often more expensive alternatives and the potential for medication errors and poor patient outcomes. Causes of drug shortages may include product quality concerns,

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FDA recognizes that some drug shortages can be neither predicted nor prevented; however, we know that effective communication and early notification from manufacturers has a significant impact on the incidence and duration of drug shortages. Manufacturers can play a critical role in decreasing the impact of shortages by reporting to the FDA circumstances that might affect their ability to supply the market and potentially lead to a drug shortage. Notifying FDA in advance of incidents that may result in a drug shortage helps FDA work with manufacturers to take early action to prevent or alleviate shortages. For example, in 2011, early notification by manufacturers allowed the FDA to help prevent shortages of 195 drugs, including 86 drugs produced by one company. However, FDA cannot begin to work with manufacturers or use the tools at our disposal to avoid or mitigate a shortage until we know there is a potential problem.

There is no single, or simple, solution that can resolve the drug shortage problem, but we are committed to working with drug manufacturers and distributors, health care providers, and other stakeholders to identify the issues that can lead to drug shortages, to enhance processes to avoid or mitigate shortages in the future, and to ensure continued patient access to vital safe and effective drugs. As part of this effort, we are issuing this guidance to help manufacturers better understand mandatory reporting obligations and to encourage voluntary reporting of additional issues that could lead to a shortage of a prescription drug or biological product.

B. Overview of Current Drug Shortage Reporting

The Agency has long recognized the significant public health impact drug shortages can have on patient care. Since 1997, section 506C has required manufacturers to notify the Agency of a discontinuance of certain drug products. Many discontinuances lead to drug shortages and can present public health concerns. Following enactment of section 506C, FDA promulgated regulations at 21 C.F.R. §§ 314.81(b)(3)(iii) and 314.91 to implement the statute. The Agency amended these regulations with the publication of the Interim Final Rule, Applications for Food and Drug Administration Approval To Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance\footnote{76 FR 78530 (Dec. 19, 2011).} on December 19, 2011 (effective January 18, 2012) (referred to in this guidance as the IFR). CDER also published a Manual of Policy and Procedures on Drug Shortage Management (CDER MAPP) to provide internal guidance to Agency staff regarding drug shortages.\footnote{CDER MAPP 6003.1, Drug Shortage Management (2006), available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM079936.pdf.}

Under section 506C, a manufacturer that is the sole manufacturer of a drug that is approved under section 505(b) or 505(j) of the FD&C Act (and that is not a product that was originally derived from human tissue and was replaced by a recombinant product) is required to notify

\begin{itemize}
  \item \footnote{76 FR 78530 (Dec. 19, 2011).}
  \item \footnote{CDER MAPP 6003.1, Drug Shortage Management (2006), available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM079936.pdf.}
\end{itemize}
FDA at least six months prior to discontinuing manufacture of the drug, if the drug is “life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition.” The FDA originally interpreted this requirement to apply only to permanent manufacturing discontinuances.

Mandatory notification under section 506C has been critical in enabling FDA to assist manufacturers in preventing or mitigating some drug shortages. For example, when notified of a discontinuance under section 506C, FDA has been able to expedite review of potential new products and suppliers and exercise regulatory flexibility for the product in shortage or an alternative product, where such action would not compromise patient safety.

However, while mandatory notification of permanent discontinuances is helpful in preventing or mitigating some drug shortages, this limited requirement is not sufficient to address the magnitude of the current drug shortage problem. In 2010, only 8% of drug shortages were due to permanent discontinuances of drug products; the majority of shortages were the result of problems at the manufacturing facility, delays in manufacturing or shipping, and API shortages. Moreover, biological products licensed through a biologics license application (BLA) under section 351 the Public Health Service Act are also vulnerable to shortages, but are not subject to mandatory reporting under section 506C. Under current law, manufacturers are therefore not required to report to FDA the majority of situations that could lead to a drug shortage.

Consequently, in response to the Executive Order, FDA published the IFR, which expands the application of our authority under section 506C to require mandatory notifications in additional circumstances, and clarifies who is responsible for notifying the Agency of a discontinuance. Moreover, in addition to mandatory notification under section 506C, to effectively work with manufacturers to more fully combat the drug shortage crisis, FDA strongly encourages companies to voluntarily notify the Agency of any other issues that could lead to a shortage of any prescription drug or biological product supplied in the U.S.

III. SCOPE AND LOGISTICS OF MANDATORY NOTIFICATION

As described in Section II.B. of this guidance, sole manufacturers are statutorily required to notify FDA of a discontinuance of manufacture of certain drug products. This section of the guidance is intended to clarify the scope and logistics of mandatory notification under section 506C and the IFR.

A. Who is Required to Notify the Agency

Under section 506C of the FD&C Act,

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if you are a sole manufacturer of a prescription drug product approved under section 505(b) or 505(j) of the FD&C Act (and that was not originally derived from human tissue and replaced by a recombinant product); and

that product is “life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition”;

then you are required by statute to notify the Agency of a discontinuance of that drug product at least six months prior to discontinuing manufacture of the product.

1. Sole Manufacturer

In the IFR, we added 21 C.F.R. § 314.81(b)(3)(iii)(d) to define “sole manufacturer” to mean “an applicant that is the only entity currently manufacturing a drug product of a specific strength, dosage form, or route of administration for sale in the United States, whether the product is manufactured by the applicant or for the applicant under contract with one or more different entities.” The definition is intended to do three things.

First, it clarifies that “sole manufacturer” means the only applicant currently supplying the U.S. market with the drug product. It does not mean the sole holder of an approved new drug application (NDA) or abbreviated new drug application (ANDA). Accordingly, a manufacturer may not rely on the Orange Book (FDA’s publication on “Approved Drug Products with Therapeutic Equivalence Evaluations”) as the source for determining whether it is a sole manufacturer. Instead, the manufacturer should use commercial data or other methods to determine whether or not it is the only entity currently manufacturing for sale in the U.S. the product in question. We emphasize that it is the manufacturer’s responsibility to determine whether it is a sole manufacturer. Manufacturers who have questions about this determination may contact the drug shortages staff. Contact information for the CDER and CBER drug shortages programs is available on FDA’s drug shortage website at http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm.

Second, the definition of sole manufacturer clarifies that the specific strength, dosage form, and route of administration of the product are critical in determining if a manufacturer is a sole manufacturer. The definition of sole manufacturer is linked to the specific strength, dosage form, and route of administration, because these characteristics may be critical for the targeted needs of particular patients. For example, a patient may be prescribed an injectable form of a particular drug product because the patient is not capable of swallowing an oral pill. If the injectable form is discontinued, the patient may be unable to continue life-saving treatment, even if the oral form is still available. Moreover, recent experience has shown that discontinuances of a specific strength, dosage form, or route of administration of a drug product may lead to a shortage of another strength, dosage form, or route of administration of the product, compounding patient difficulties in obtaining the drug product. For instance, in the previous example, if the oral form of the drug product is discontinued, providers may prescribe the injectable form to all patients. This increase in demand for the injectable form of the product may cause a shortage of the injectable form. If the FDA is notified in a timely manner of the
discontinuance of the oral form, we may be able to work with manufacturers and other stakeholders to avoid, or mitigate the impact of, a shortage of both formulations of the product. Accordingly, to enable the Agency to work most effectively with manufacturers and other stakeholders to prevent or mitigate potential shortages, discontinuances of a specific strength, dosage form, or route of administration of drug products subject to section 506C must be reported to us.\textsuperscript{11}

Third, the IFR makes clear that it is the application holder of the drug product subject to section 506C who bears the responsibility for reporting a discontinuance to the Agency. For purposes of section 506C, an application holder will be considered a “manufacturer” even if the application holder contracts that function out to another entity. The application holder is responsible for establishing processes with contract manufacturers that ensure the application holder’s compliance with section 506C and the IFR. For example, Company X holds an NDA for a drug product subject to section 506C. Company X contracts with Company Y to manufacture the drug product for the purposes of marketing and selling the drug product in the United States. Company X would be considered the “sole manufacturer” and would be required to establish a process with Company Y that ensures Company X’s ability to report a discontinuance of the drug product to FDA.

The intention of section 506C is to alert FDA to possible disruptions in supply of certain drug products important to patient care to allow us to work with the manufacturer or others to minimize, to the extent possible, disruptions in patient access to those products. Considering this intention, we encourage manufacturers to be over-inclusive when determining whether they are a sole manufacturer. To best serve patients and protect the public health, the Agency should not be under-informed of information related to discontinuances. The Agency is better positioned to assist in preventing or mitigating a drug shortage that may be caused by a discontinuance if it is armed with all available information.

2. “Life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition.”

Section 506C of the FD&C Act requires reporting of discontinuances of drugs that are “life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition.” In 2007, the Agency interpreted “life-supporting or life-sustaining” to mean “a drug product that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.” We have interpreted “debilitating disease or condition” to mean “a serious disease or condition.”\textsuperscript{12} FDA should therefore be notified under section 506C if a drug product that is used to treat or prevent a serious disease or medical condition is discontinued.

Again, to enable FDA to be fully informed, we encourage manufacturers to be over-inclusive when determining whether a particular product is subject to mandatory notification under section 506C.

\textsuperscript{11} 21 CFR 314.81(b)(3)(iii)(d), as amended by the IFR (76 FR 78530, 78540 (Dec. 19, 2011)).
\textsuperscript{12} 72 FR 58993, 58994 (Oct. 18, 2007).
B. What Information to Report to the Agency

Under section 506C, sole manufacturers are required to notify FDA of a discontinuation of a drug product subject to section 506C. Previously, FDA indicated that a discontinuation did not include planned or unplanned temporary manufacturing cessations. Only manufacturers who intended to permanently discontinue manufacture and marketing of the drug were subject to the mandatory notification requirements.\(^\text{13}\) In the IFR, however, we revise this policy position and define the term “discontinuance” to mean “any interruption of manufacturing of a drug product described in paragraph (b)(3)(iii)(a) for sale in the United States that could lead to a potential disruption in supply of the drug product, whether the interruption is intended to be temporary or permanent.”\(^\text{14}\) Thus, the term “discontinuance” now includes both temporary and permanent interruptions in manufacturing, if the interruption could lead to a disruption in supply of the product.

Any permanent discontinuance of manufacturing by a sole manufacturer will lead, per se, to a disruption in supply of the product; thus, all permanent discontinuances must continue to be reported to FDA.\(^\text{15}\) Temporary discontinuances must be reported to the Agency only if the discontinuance reasonably could be expected to lead to a disruption in supply of the product. For example, the following circumstances would trigger notification to the FDA of a discontinuance of a drug product subject to section 506C:

- A business decision to permanently discontinue manufacture of a drug product;
- A delay in acquiring API or inactive ingredients that leads to, or could lead to, a temporary interruption in manufacturing of a drug product while alternative suppliers are located;
- Equipment failure or contamination affecting the quality of a drug product that necessitates an interruption in manufacturing while the equipment is repaired or the contamination issue is addressed;
- Manufacturing shut-downs for maintenance or other routine matters, if the shut-down extends for longer than anticipated or otherwise could disrupt supply of a drug product.

Conversely, a manufacturer would not be required to notify FDA if a discontinuance is part of the normal manufacturing schedule and is not expected to lead to a disruption in supply of a drug product subject to section 506C. For example, FDA need not be notified in the following circumstances:

- The manufacturer uses the same manufacturing plant to manufacture two drug products, one of which (Product A) is subject to section 506C. From January to

\(^{13}\) 72 FR 58993, 58995 (Oct. 18, 2007).
\(^{14}\) 21 CFR § 314.81(b)(3)(iii)(d), as amended by the IFR (76 FR 78530, 78540 (Dec. 19, 2011)).
\(^{15}\) Id.
June of each year the manufacturer uses the plant to produce Product A. From July to December of each year the manufacturer uses the plant to produce Product B. Although this could be considered a temporary discontinuance of Product A from July to December, because this is the usual manufacturing schedule and should not therefore result in a disruption in the supply of Product A, the manufacturer need not notify the Agency of the annual, temporary discontinuance of Product A.

- A manufacturer of a drug product implements a scheduled shutdown of its manufacturing facility each year for routine maintenance. The annual shutdown is anticipated and planned for in advance; therefore, it is not expected to disrupt supply of a drug product subject to section 506C. The shutdown does not need to be reported to the Agency under section 506C.

- A manufacturer of a drug product subject to section 506C experiences an unexpected power outage that results in an unscheduled interruption in manufacturing. The manufacturer expects to resume normal operations within a relatively short timeframe and does not expect a disruption in the supply of the drug product. The shutdown does not need to be reported to the Agency under section 506C.

If any of the circumstances described above do lead to a disruption in supply of the drug product, even if unanticipated, then it becomes a reportable discontinuance and the manufacturer would be required to notify FDA of a discontinuance of the product under section 506C. For example, if a scheduled or routine manufacturing shutdown continues for longer than expected, such that demand cannot be met with current inventory of the product, this would be a disruption in supply of the product and the shutdown would become a reportable discontinuance under section 506C.\(^\text{16}\)

We revised our policy position to include temporary interruptions in manufacturing in the definition of discontinuance based on experience showing that even temporary discontinuances can have a significant impact on patient access to drug products. Moreover, this broader interpretation of the statutory language will expand FDA’s ability to distribute information on the discontinuance of certain drugs to physician and patient organizations and better enable FDA to work with manufacturers and other stakeholders to respond to potential drug shortages.

Manufacturers are responsible for determining whether a particular situation falls within the mandatory reporting requirements of section 506C. If you are facing an actual or potential discontinuance and are unsure whether it must be reported under the regulation, you may contact the drug shortages staff in the relevant Center by e-mail or by phone at the contact information available on the Agency’s drug shortages website. Again, we encourage over-inclusiveness.

\(^\text{16}\) 21 CFR 314.81(b)(iii)(3)(d), as amended by the IFR (76 FR 78530, 78540 (Dec. 19, 2011)). We understand that a manufacturer may be unable to report some temporary discontinuances six months in advance, as required by statute. The timing of reporting unplanned temporary discontinuances in discussed in Section III.C., below.
when determining whether a particular situation falls within the scope of mandatory reporting requirements.

C. When and How to Notify the Agency

1. Six Month Notification Period & Certifications of “Good Cause”

Section 506C requires manufacturers to notify the Agency at least six months prior to discontinuing manufacture of a drug product subject to section 506C. The six month period may be shortened if the FDA finds “good cause” exists for the reduction based on information submitted to the Agency by the manufacturer in a certified written request. We emphasize that the manufacturer must notify the Agency at least six months prior to the discontinuance unless: 1) the manufacturer has submitted a written certification of “good cause”; and 2) the Agency has affirmatively made a determination to allow a reduction in the notification period for one of the good cause reasons listed in 21 C.F.R. § 314.91(d), including if:

(1) a public health problem may result from continuation of manufacturing for the 6-month period;
(2) a biomaterials shortage prevents the continuation of the manufacturing for the 6-month period;
(3) a liability problem may exist for the manufacturer if the manufacturing is continued for the 6 month period;
(4) continuation of the manufacturing for the 6-month period may cause substantial economic hardship for the manufacturer;
(5) the manufacturer has filed for bankruptcy under chapter 7 or 11 of title 11, United States Code (11 U.S.C. 701 et seq. and 1101 et seq.);
(6) the manufacturer can continue distribution of the drug product to satisfy existing market need for 6 months; or
(7) other good cause exists for the reduction.

The only exception to this requirement is if a manufacturer is unable to notify us of a temporary discontinuance six months prior to the discontinuance because it was an unforeseen occurrence (e.g., unexpected contamination). Under those circumstances, a manufacturer need not submit a written certification of good cause requesting a reduction in the notification period. Instead, the manufacturer must notify us as soon as possible after it knows that a discontinuance will occur. In any other instance, a manufacturer seeking a reduction in the six-month notification period must submit a written certification of good cause and obtain affirmative Agency approval of the reduction in the notification period.

2. Procedures for Notifying the Agency of a Discontinuance and for Submitting a Certification of “Good Cause”

Telephone calls or electronic communication are often the fastest and most efficient methods for conveying important information. The Agency already receives many reports of discontinuances

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17 21 CFR 314.91.
18 Id.
and potential drug shortages via phone and e-mail. To reflect this practice, the IFR requires manufacturers to report a notice of a discontinuance to FDA either electronically or by telephone according to instructions on the FDA’s drug shortages website at http://www.fda.gov/Drugs/DrugSafety/DrugShortages. As indicated on the website, products regulated by CDER should be reported to the CDER Drug Shortages Coordinator, and products regulated by CBER should be reported to the CBER Products Shortage Coordinator.

Certifications of good cause must continue to be submitted according to the procedure outlined in 21 C.F.R. § 314.91.

IV. SCOPE AND LOGISTICS OF VOLUNTARY NOTIFICATION

Given the magnitude of the drug shortage crisis in the U.S., and the limited scope of mandatory notification under section 506C, the FDA sent a letter to manufacturers of prescription products on October 31, 2011, encouraging them to voluntarily notify the Agency of any potential disruption to supply of a prescription product that could reasonably be expected to lead to a product shortage, beyond those circumstances required to be reported by statute. Unlike mandatory notification, voluntary notification includes prescription biological products licensed under a BLA. Voluntary notifications will improve FDA’s knowledge of potential and existing drug and biological product shortages, allowing us to more effectively work with manufacturers to prevent or mitigate shortages. This section provides guidance on the scope and logistics of the voluntary notification process.

A. Who Should Notify the Agency

The Agency encourages manufacturers of all prescription drug or biological products to voluntarily notify the Agency of issues that may result in a shortage or potential disruption in supply of that product in the U.S. market. We encourage you to notify the FDA even if you are not a sole manufacturer of a drug or biological product, as described in relation to mandatory reporting under section 506C. Moreover, we encourage voluntary notification for all prescription drug and biological products.

B. What Information to Report to the Agency

Voluntary notification of issues that may lead to a potential shortage or disruption in supply includes reporting of circumstances beyond those instances (i.e., discontinuance) that are required to be reported by section 506C. Shortages and disruptions in supply may arise from a wide range of factors other than a manufacturer’s decision to discontinue a product. FDA encourages manufacturers to notify the Agency’s drug shortages staff of the following issues if they reasonably could be expected to lead to a potential shortage or disruption in supply of a prescription drug or biological product:

- product quality problems, such as the presence of particulates or impurities, microbial contamination, and stability concerns;
Draft – Not for Implementation  
Contains Nonbinding Recommendations

- interruptions or other adjustments in manufacturing that temporarily halt production and that may adversely affect market supply, such as renovation of manufacturing facilities;

- delays in acquiring critical raw materials or components, or loss of raw material or components (e.g., vials, stoppers, bottles) suppliers;

- transfer of manufacturing to an alternate facility (e.g., due to loss of an existing manufacturing site or to add additional capacity);

- loss of a production line or production capacity (e.g., machinery failure or malfunction or quality issues related to a cell line);

- any production problems that occur during or after manufacturing that could result in supply disruptions (e.g., out of specification test results, stability problems, or labeling and packaging defects);

- import delays (e.g., shipments detained upon entry to the U.S. for any reason that may delay delivery to the manufacturing firm);

- unexpected increases in demand (e.g., due to a shortage of an alternative product); and

- product discontinuances (e.g., a business decision to stop manufacturing or marketing the product or a temporary product hold while investigating issues that may result in a recall), even if you are not a sole manufacturer or the product in question is not subject to section 506C.

This is not an exhaustive list of circumstances that may result in a shortage or potential disruption in supply of a prescription drug or biological product and does not change manufacturers’ responsibility to report issues to the Agency under other applicable regulations. We reiterate that FDA encourages manufacturers to be over-inclusive and to report any issue that reasonably could be expected to have an impact on the manufacturer’s ability to supply the market and/or could lead to a product shortage.

C. When and How to Notify the Agency

Early notification is critical to the Agency’s ability to respond effectively to potential shortage situations. Manufacturers should notify the Agency as soon as the manufacturer becomes aware of an issue that may result in a product shortage. The sooner FDA is notified, the better the chance of averting shortages of important products and minimizing disruptions in patient access to the product.

Manufacturers should notify FDA either electronically or by telephone according to instructions on the FDA’s drug shortages website at [http://www.fda.gov/Drugs/DrugSafety/DrugShortages](http://www.fda.gov/Drugs/DrugSafety/DrugShortages). As
noted on the website, products regulated by CDER should be reported to the CDER Drug Shortages Coordinator, and products regulated by CBER should be reported to the CBER Products Shortage Coordinator.

V. WHAT FDA DOES WITH INFORMATION REPORTED

Communication and cooperation between the Agency and industry is vital to successfully combating the drug shortage crisis. The best way for FDA to become aware of potential drug or biological product shortages is for industry to notify us of potential problems as soon as possible. Once FDA is notified of any incident that could result in a product shortage, whether a required notification of a discontinuance under section 506C or a voluntary notification, the Agency will work closely with the manufacturer to help prevent a shortage. FDA may undertake a variety of actions to help prevent or mitigate a product shortage, including the following:

- Expedite review of submissions from manufacturers. These submissions may support a marketing application for a new product (an NDA, ANDA, or BLA), may support a manufacturing change that will allow a product to be available (for example, a chemistry supplement for a new manufacturing site), or may involve other issues (for example, toxicity data for an impurity identified in a product). FDA makes every effort to prioritize review and inspections needed for any change that will help mitigate a product shortage. FDA also communicates with foreign regulators as appropriate.

- Identify additional sources of supply or alternate manufacturers that can initiate or ramp-up production. For example, if the manufacturer has data to support extension of the expiration dating for certain inventory, FDA may review the data and consider appropriate action, such as exercising regulatory discretion for use of a product beyond its labeled expiration date. In addition, if another safe and effective product is available, FDA may work with other manufacturers to supply that product to patients during a shortage.

- Find new/additional sources of raw material. If the shortage is due to an inadequate supply of API or other raw materials, FDA can work with the manufacturer, as appropriate, to identify and approve new API suppliers or alternative suppliers of other raw materials.

- Consult with and advise sponsors on resolution of manufacturing or quality issues. FDA can work with the manufacturer to address issues as quickly and safely as possible.

- Exercise regulatory discretion for the temporary importation of a non-U.S. product, in rare instances. Temporary importation of foreign drugs is considered in rare cases when there is a shortage of an approved U.S. drug that is important to patients and the shortage cannot be resolved by manufacturers of the approved U.S. drug in the immediate future. In these cases, FDA searches for companies that manufacture drugs for foreign markets to determine whether such sources may help meet critical patient needs in the U.S. When a firm is located that is willing and able to import a foreign drug, FDA evaluates
the overseas drug to ensure that it is of adequate quality and that the drug does not pose significant risks for U.S. patients. The information about the imported product and how patients can access supplies is posted on the FDA Drug Shortage website along with the Dear Healthcare Professional letter from the company that is importing the product.

Using these strategies, FDA is able to help prevent many drug shortages each year. We recognize, however, that not all drug shortages can be prevented. For example, some shortages involve unanticipated problems such as a manufacturing line breakdown that will take some time to resolve; if other manufacturers are unable to make up a production shortfall, an unavoidable shortage may occur. Similarly, some problems such as bacterial contamination or dangerous particulates in injectable products may involve risks that are too significant and would cause patient harm. In cases where a shortage cannot be avoided entirely, FDA’s goals are to minimize the effect on patients of the shortage by getting product back to the market as quickly and safely as possible.

FDA also communicates information to the public about shortages based on information provided by manufacturers. FDA posts information about all actual shortages on the FDA drug shortages website. When manufacturers of products in shortage report updates to the Agency, FDA posts information on shortages on the FDA drug shortages website. FDA also responds to consumer inquiries through the e-mail account drugshortages@fda.hhs.gov to keep the health care community up to date on shortage situations. However, FDA does not post on its website information regarding potential shortages, because we are sensitive to the possibility that this could lead to increased stockpiling of a product facing a potential shortage, possibly worsening the situation. Potential shortages may never progress to actual shortages if the efforts that manufacturers and FDA undertake to help prevent the shortage are successful. In addition, when communicating with healthcare providers, patients, and other third parties, FDA does not disclose trade secret or confidential commercial information that we receive from manufacturers in connection with a drug shortage unless authorized by law.19


VI. ADDITIONAL CONSIDERATIONS FOR MANUFACTURERS

Manufacturers play a primary role in preventing or responding to drug or biological product shortages, because they make the products needed by doctors and patients. In addition to early notification to the FDA of issues that may result in a shortage or potential disruption in supply, manufacturers can engage in other actions that may help prevent some shortages.

For example, many drug shortages arise from quality or other issues experienced during the manufacturing process. It is a primary responsibility of manufacturers to maintain their compliance with current good manufacturing practice (CGMP) requirements and to ensure that their suppliers of ingredients, components, and substances used in the manufacture of their

19 See, e.g., 18 USC 1905; 21 USC 301(j); 21 CFR Part 20.
products meet standards of safety and quality sufficient to ensure that the final drug or biological product is safe and effective. Adequate attention to this responsibility, including by implementation of well-defined risk management systems at all layers of the supply chain, and through continuous evaluation and investment in manufacturing operations will help avoid many manufacturing problems that lead to product shortages.

Contingency planning by manufacturers may also help prevent some shortages. Analysis of 127 drug shortages between January 1, 2010 and August 26, 2011 showed that approximately 60% of the shortages were caused by circumstances that may have been avoided or mitigated if the manufacturer had undertaken enhanced redundancy or contingency planning.20 We encourage manufacturers to make contingency plans for responding to situations that could lead to a shortage. This could include building redundancy into manufacturing capabilities, establishing relationships with and adequate controls over contract manufacturers, and/or identifying and seeking approval for alternative API and component suppliers. FDA is available to discuss with industry contingency plans for additional manufacturing sites, production lines, and suppliers to help prevent shortages. When contemplating such contingency plans, the sponsor should contact the FDA Office and specific review division with regulatory responsibility for the product in question. When contacting any of these offices, we recommend that the sponsor make clear its intention to build additional capacity or develop other contingency plans to be better prepared to prevent potential product shortages.

Shipments From Abroad to Help Ease Shortage of Two Cancer Drugs

By GARDINER HARRIS

WASHINGTON — Dire shortages of two critical cancer drugs — shortfalls that have threatened the lives and care of thousands of patients — should be resolved within weeks, federal drug officials said.

The two drugs are Doxil and methotrexate, and in both cases supplies in the United States are being bolstered by shipments from abroad. Shortages of scores of other drugs continue.

“We’re not out of the woods,” said Dr. Sandra L. Kweder of the Food and Drug Administration’s drug center. “But these two particular shortages have been very, very upsetting to patients and to us.”

Dr. Peter C. Adamson, chairman of the Children’s Oncology Group, which is financed by the National Cancer Institute, said he was pleased that the immediate threat of a methotrexate shortage had passed. “But this is at best a Band-Aid approach to the problem,” he said.

Shortages of both drugs developed when Ben Venue Laboratories temporarily closed its manufacturing facility in Bedford, Ohio, because it could not guarantee product safety.

In the case of Doxil, which is used to treat ovarian cancer, multiple myeloma and AIDS-related Kaposi’s sarcoma, the F.D.A. has decided to allow temporary shipments from India of Lipodox, which is similar to Doxil and is made by Sun Pharma Global.

And the pharmaceutical company Hospira is rushing 31,000 vials — enough to last the entire nation a month — of preservative-free methotrexate from its plant in Australia to the United States. Hospitals began receiving the drug, which is vital in the treatment of a common form of childhood leukemia, on Tuesday. The F.D.A. has also hastened the approval of an application by APP Pharmaceuticals to manufacture methotrexate, an application that has languished since 2010.
There is a years-long backlog of applications for new generic drugs at the F.D.A. because the government does not have the money to hire enough reviewers to analyze the applications or inspectors to visit the facilities, many of them abroad. The generic drug industry tired of waiting for Congress to fully finance the F.D.A.’s generic drug office and this year proposed providing the agency with $299 million in annual fees to finance the review process.

Dr. Kweder said the agreement on generic drug fees — part of a package of F.D.A. fee proposals that Congress is expected to consider in the coming months — should eventually help prevent some drugs from going into short supply.

The F.D.A. on Tuesday also released a lengthy list of instructions for drug companies to follow when their manufacturing of critical medicines is threatened. At least 180 drugs, a record number, have been in short supply at one time or another over the past year. President Obama issued an executive order last year that was intended to ameliorate the situation; it requires drug companies to alert the F.D.A. when potential problems threaten supplies. Legislation on the issue is also pending in Congress.

The causes of the shortages are multiple.

Dr. Adamson called on the F.D.A. to create an advisory committee of experts from across medical disciplines to assess which drug shortages were most acute.

“Children are at such risk from drugs in short supply that it doesn’t give me a whole lot of comfort that we’ve moved past one or two of these shortages,” Dr. Adamson said. “What about the next one? And the one after that?”
**Drug Shortages**

**FDA Relies On Importation, Fast Approval And Early Reporting to Combat Shortages**
*By Conor Hale and Paul Goldberg*

FDA announced a series of measures to combat shortages of generic drugs in oncology.

At a briefing Feb. 21, the agency said it has:
- Allowed the temporary importation of an Indian-made drug to relieve shortages of Doxil (doxorubicin hydrochloride liposome injection). Despite being on the market, the imported drug, Lipodox, will remain unapproved in the U.S.
- Averted a shortage of methotrexate after the drug’s manufacturer, Ben Venue Laboratories, suspended operations at its production facility. FDA expedited the review of an alternative manufacturer’s application for preservative-free methotrexate.
- Published a draft guidance requesting an increase in voluntary notifications of shortages by the industry. Sole producers of drugs deemed “life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition” are already required to notify the agency about impending shortages. The draft guidance applies to situations where multiple makers exist.

(Continued to page 2)

**Guest Editorial**

**FDA Must Address Economic Incentives To Resolve Drug Shortages Permanently**
*By Rena Conti*

The FDA’s actions earlier this week are an important first step in ensuring the supply of medically necessary drugs.

To attain the long term policy goals of adding domestic manufacturing capacity to produce medically necessary drugs at competitive prices—accessible by all purchasers in the U.S. market—will require the pursuit of complementary policies mindful of intended and unintended consequences.

(Continued to page 6)

**The Duke Scandal**

**South Carolina Clinic, Potti Part Ways**
*By Paul Goldberg*

Anil Potti doesn’t work at the Coastal Cancer Center anymore.

The Myrtle Beach practice, which employed the disgraced cancer researcher who had claimed to be a Rhodes Scholar, said his last day at work was Feb. 21, just short of one year from when he began in March 2011.

(Continued to page 7)
had undertaken enhanced redundancy or contingency planning.” The guidance encouraged manufacturers to contact the agency if they plan on developing new contingency plans to discuss additional manufacturing sites, production lines and suppliers.

“Through the collaborative work of FDA, industry, and other stakeholders, patients and families waiting for these products or anxious about their availability should now be able to get the medication they need,” said FDA Commissioner Margaret Hamburg.

“We’ve increased staff in the FDA drug shortage program. We now have 11 full-time staff working on this problem. A broader group of individuals step in as needed—doctors, scientists, inspectors, and members of our offices of generic drugs and compliance.

“Our actions include the continued development of a tracking database for drug shortages, and sharing the information with the Justice Department to address issues of stockpiling, so-called gray markets, and exorbitant pricing of drugs that are in short supply,” said Hamburg.

**Doxil and Methotrexate**

“Over the past 24 months, it’s become very clear that what causes the drug shortage program is multifactorial,” said Len Lichtenfeld, deputy chief medical officer of the American Cancer Society. “What causes the shortage for one drug may not be the cause for another drug.

“However that doesn’t make life any easier for the parents of children with cancer who may not be able to get methotrexate. Or for doctors who cannot treat the children or adults with other forms of leukemia, because they can’t drugs such as cytarabine. Or, for that matter, for ovarian cancer patients who are not able to get Doxil.”

“The current drug shortage has become a daily nightmare for patients, their families, and those who treat them,” he said. “And as we have researched and worked to try and identify solutions to this issue, it has become very clear that there is unfortunately not one simple solution.”At the briefing earlier this week, the agency focused on the management of shortages of two cancer drugs: Doxil and methotrexate.

Doxil is used in multiple treatment regimens, including treatment of ovarian cancer after failure of platinum-based chemotherapy. The drug is also indicated for use in AIDS-related Kaposi’s sarcoma and multiple myeloma.

“Lipodox, supplied by Sun Pharma Global FZE and its authorized distributor, Caraco Pharmaceutical
Laboratories, will be available starting today,” said Hamburg Feb. 21.

Lipodox will serve as a substitute for Doxil. FDA’s exercise of enforcement discretion is a temporary, limited arrangement specific to these companies. Lipodox is manufactured in India.

“Lipodox remains unapproved by FDA for the U.S. market—but when a critical drug is unavailable, and a substitute can produce a comparable outcome, and it has been evaluated by us for quality and for safety—we use our enforcement discretion to allow for its temporary and limited use,” said Hamburg.

The agency said that temporary importation of unapproved foreign drugs is considered in rare cases when there is a shortage of an approved drug that is critical to patients and the shortage cannot be resolved in a timely fashion with FDA-approved drugs.

When a company is identified that is willing and able to import the needed drug product, FDA evaluates the foreign-approved drug to ensure that it is of adequate quality and that the drug does not pose significant risks for U.S. patients.

To combat the shortage of methotrexate, a drug used to treat many forms of cancer and other serious diseases, FDA engaged many firms to assist in maintaining supplies.

One formulation of the drug—preservative-free methotrexate—is used in the intrathecal treatment of children with acute lymphocytic leukemia and for high-dose therapy of osteosarcoma.

The Feb. 21 panel included Sara Stuckey—whose six-year-old son, Nate, was diagnosed with ALL in 2009, and has since been undergoing treatment with methotrexate. Nate goes through treatment once every three months.

Recently, the Stuckey family was told that their clinic only had enough methotrexate for Nate’s next treatment—and that after that they might have to seek other options, due to shortages of the drug.

“I can assure you that the conversation of telling parents about their child’s cancer diagnosis is very difficult, but the distress of this conversation was always alleviated somewhat because, in most cases, I was able to tell them about the very effective therapy that we had available, and the realistic chance that their child would be cured,” said panel member Michael Link, president of the American Society of Clinical Oncology. “This conversation has recently changed.”

“Telling parents that, with years of research, we have developed the recipe to treat their child’s cancer—but that the essential ingredients are unavailable today—is unimaginably painful,” said Link.

The shortage became inevitable when methotrexate’s sponsor, Ben Venue, said it would shut down production of the drug. The circumstances leading up to that decision are the subject of a congressional investigation.

FDA said it worked with Ben Venue to release already manufactured preservative-free methotrexate.

Also, FDA prioritized review and then approved a preservative-free methotrexate manufactured by APP Pharmaceuticals. APP’s application for preservative-free methotrexate was a supplement to its previously approved generic drug application, which the firm had previously discontinued.

“When we were first informed of the shortage of methotrexate injection, we took a two-pronged approach,” said panel member Mitchell Ehrlich, vice president of quality assurance at APP.

“First, we began the process of significantly increasing production of the preservative-containing methotrexate injection, taking our output over the course of the next few weeks to nearly four times our historical rate.

“Second, we worked collaboratively with the [FDA Center for Drug Evaluation and Research]’s drug shortage program to expedite approval of our pending application for preservative-free methotrexate injection,” said Ehrlich.

“As soon as we received notification of the approval, we immediately began the process of scheduling production, so that in the next four to six weeks we will able to supply clinicians with this critically needed drug.”

Hamburg said the APP product would become available in March.

“[APP] responded promptly to our outreach on the need for more preservative-free methotrexate, and expedited standing up new manufacturing capacity,” said Hamburg. “FDA prioritized their application, as we do for any drug in short supply.”

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Another company, Hospira Inc., also expedited the release of additional supplies of the drug, resulting in 31,000 vials of new product—enough for one month’s worth of demand—and began shipping to hundreds of U.S. hospitals and treatment centers.

FDA is also working with other manufacturers—Mylan and Sandoz Pharmaceuticals—in order to meet demand, the agency said.

“Our ability to increase methotrexate production is contingent upon two things: additional active ingredient and streamlined systems for production,” said Michael Ball, CEO of Hospira. “Working in close cooperation with the FDA, we were able to achieve both.”

“As we speak, we are transporting over 100 kilos of active ingredient from locations from around the world to our manufacturing facility. As a result, next week we will release an additional 34,000 vials, another month’s worth of inventory, to meet the full market demand.

“In mid-March, we will release another 55,000 units—which will meet the market’s full demand, but also keep a safety stock on hand,” he said.

“The agency’s rapid response has been unbelievable in this entire situation, and they have been tireless in their efforts to help us avert further shortage situations.”

Permanent Solutions

Many panel members made direct calls to Congress to pass legislation addressing the drug shortage problem.

“Let me give a few names: cisplatin, doxorubicin, daunorubicin, etoposide, leucovorin, thiopeta, vinblastine,” said Peter Adamson, chair of the Children’s Oncology Group. “These are all anti-cancer drugs discovered 30, 40 years ago. Each of those drugs is an essential part of curing childhood cancer. They all continue to be on the FDA drug shortage list. There are potential future crises waiting to happen.”

“ASCO believes there are three critical elements that must be part of the long-term solution,” said Link. “First, FDA needs to have information on manufacturing delays or market withdrawals as far in advance as possible.

“Second, we have to address the role that economics plays in causing shortages. For a variety of reasons, the market is unable to respond in expected ways when there is high demand and limited supply of generic medications. Addressing this aspect of drug shortages, including pricing and incentives to ensure manufacturers incorporate redundancies and contingency planning in their production, is a necessary and critical aspect of any solution.

“And third, the generic user fee plan must be passed to provide resources for reviewing applications in a timely way. This will also enable FDA to complete inspections and work with companies to address issues that might otherwise lead to shortages.”

“The data is clear that early notification has a significant and meaningful impact on drug shortages,” said Hamburg. “We fully support bipartisan legislation to require finished product manufacturers to report all prescription drug shortages to the FDA, and to give FDA new authority to enforce these requirements.”

Legislation should be introduced rapidly, COG’s Adamson said.

“I certainly understand that passing legislation is complex. It is difficult,” said Adamson. “I suspect, however, that it is no more difficult than curing a child with cancer. And I can absolutely tell you that it is no more complex or difficult than what children every day face in their fight against childhood cancer.

“We can induce a remission in a child with ALL within four weeks’ time. That’s the first step towards cure. It’s complex treatment. It’s difficult treatment. But if we can induce a remission in children with leukemia within four weeks, I would challenge our colleagues in Washington to enact legislation in four weeks’ time.”

Congressional Letter to Ben Venue

In a related development, a group of Senators wrote a letter to Ben Venue Laboratories Feb. 16, seeking information about the company’s role in the methotrexate shortage.

“We are deeply troubled by recent reports of the acute and prevalent shortages of Methotrexate as well as other lifesaving drugs for patients across the country,” wrote Sens. Richard Blumenthal (D-Conn.), Tom Harkin (D-Iowa), Mike Enzi (R-Wyo.), Lamar Alexander (R-Tenn.), and Bob Casey (D-Pa.).

“While Ben Venue has publicly stated that supplies of methotrexate will become available in stages and that certain portions of its plant will return to production in the first quarter of 2012, no timeline has been given to patients and providers with specific information as to when production of methotrexate will fully resume, and how much product will be available in the meantime.”

The senators requested responses to a number of questions, including which “significant manufacturing and quality concerns” led the company to suspend production; the relationship among Boehringer Ingelheim, Bedford Laboratories and Ben Venue Laboratories as it relates to production and distribution of Methotrexate, as well as the factors that led Bedford
to suspend the distribution of all Ben Venue products; the date on which the company first reported the need to suspend production of methotrexate to FDA and what actions the company has subsequently taken to work with FDA to mitigate the adverse consequences of this suspension; and the company’s timeline for restoring full manufacturing capacity for methotrexate.

Harkin is the chairman of the Senate Health, Education, Labor, and Pensions Committee; Enzi is the ranking member; and Blumenthal, Alexander, and Casey are committee members.

The text of the letter follows:

George Doyle III, President and Chief Operating Officer
Ben Venue Laboratories
c/o Bedford Laboratories
300 Northfield Road
Bedford, OH 44146

Dear Mr. Doyle,

We are deeply troubled by recent reports of the acute and prevalent shortages of Methotrexate as well as other lifesaving drugs for patients across the country. As you know, Methotrexate is a generic product that is used by millions of Americans to treat pediatric leukemia as well as severe autoimmune conditions. Recent reports, including an article this weekend in The New York Times, have indicated that Ben Venue Laboratories—one of the nation’s largest suppliers of injectable preservative-free Methotrexate—voluntarily suspended operations at its Bedford, Ohio, plant in November because of “significant manufacturing and quality concerns.”

Of even greater concern, these same reports also indicated that the publicly available supply of these drugs may be exhausted within the next few weeks. While Ben Venue has publicly stated that supplies of Methotrexate will become available in stages and that certain portions of its plant will return to production in the first quarter of 2012, no timeline has been given to patients and providers with specific information as to when production of Methotrexate will fully resume, and how much product will be available in the meantime.

Given the nature of this shortage, the serious health impacts it is having at the state and national levels, as well as Congress’ ongoing efforts to address such drug shortages, we would request that you please provide the following information by Feb. 24, 2012:

1. The specific “significant manufacturing and quality concerns” that led your company to suspend production, including what preventative maintenance and re-qualifications of equipment were overdue as noted in your Dec. 23, 2011 press release;
2. Copies of any inspection findings regarding your facility by FDA, EMEA and/or any other global agencies as referenced in your Dec. 23, 2011 press release;
3. The date on which Company management learned of these concerns and how they were brought to your attention;
4. The relationship among Boehringer Ingelheim, Bedford Laboratories and Ben Venue Laboratories as it relates to production and distribution of Methotrexate, and the factors that led Bedford to suspend the distribution of all Ben Venue products;
5. The date on which your company first reported the need to suspend production of Methotrexate to the Food and Drug Administration and what actions your company has subsequently taken to work with the Food and Drug Administration to mitigate the adverse consequences of this suspension;
6. A description of what other actions your company has taken to address the identified “significant manufacturing and quality concerns;”
7. Your company’s timeline for restoring full manufacturing capacity for Methotrexate, including whether it can be manufactured other than in the North facility (described in your December 2011 press release as being unavailable until fourth quarter 2012), and how your company intends to allocate available stock until prior capacity is restored; and
8. Whether you believe that reimbursements for Methotrexate played a factor in the current overall shortage. As part of your answer please provide the quarterly reported Average Sales Prices (ASP), total annual revenues, total annual sales, and production costs for the previous two years associated with your sales of Methotrexate.

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Guest Editorial

Econ 101: Drugs in Short Supply Should Command Higher Prices
(Continued from page 1)

The agency announced a threefold approach to increase the supply of cancer drugs in shortage:

First, Lipodox will be imported to replace supply of the cancer drug Doxil. FDA’s ability to arrange limited, temporary importation of Lipodox supplies is firmly within their regulatory purview.

Second, the FDA has approved a new manufacturer of preservative-free formulation of methotrexate, APP Pharmaceuticals Inc.

Third, in response to President Obama’s Oct. 31, 2011 executive order on prescription drug shortages, the FDA issued draft guidance to industry on detailed requirements for both mandatory and voluntary notifications to the FDA of issues that could result in a drug shortage or supply disruption.

These policies should be lauded as striking a good balance between the short-run benefits of tailoring regulatory responses to meet urgent patient needs against safety concerns, and the potential long-term reductions in competition.

For example, the contract between the FDA and Sun Pharma Global FZE and Caraco Pharmaceutical Laboratories Ltd. to provide Lipodox will increase the supply of treatments for specific, cancer-affected, vulnerable patient populations in the short term.

Lipodox is expected to be available for distribution in the U.S. in the next couple of weeks. While importation has been vilified by commentators as placing the U.S. population at risk from the consumption of “low quality drugs,” this concern may be mitigated in this example.

Sun Pharma manufactures Lipodox in a manufacturing facility in Halol, India. To approve the sale in the U.S. market, the FDA must, by statute, complete an independent evaluation of the drug and the supplier’s manufacturing facilities to ensure that the drug is of adequate quality, and will not pose significant health risks for U.S. patients.

Only after the successful evaluation of these factors may the FDA exercise its “executive discretion” to allow the importation of a foreign drug into the U.S. market.

The FDA’s importation policy is limited by duration and in scope to a drug widely considered to be “medically necessary.” If the duration of the Lipodox supply were to be extended, then FDA should release details of the periodicity of drug and facility inspections to the public, to alleviate quality concerns.

The temporary and limited nature of the importation contract between the FDA and Sun Pharma suggests the supply of Doxil may become short again if no domestic manufacturers are able or willing to increase production in the near term. Clarity on other actions the FDA might be pursuing to increase the willingness and ability of domestic manufacturers to supply Doxil is needed.

The FDA’s policy on preservative-free methotrexate will also increase supply of this “medically necessary” drug by multiple manufacturers. APP expects their new supply of preservative-free methotrexate to become available in March.

In the meantime, the FDA has been working with Ben Venue to release already manufactured preservative-free methotrexate, following the FDA’s confirmation of its safety. This supply is currently available.

In addition, Hospira has announced the expedited release of additional supplies, resulting in 31,000 vials of new product, being shipped to U.S. hospitals and treatment centers this week. FDA reports they are actively working with other manufacturers of methotrexate to increase production in order to meet patient demand.

Finally, the additional policies adopted by the FDA to encourage the voluntary and mandatory notification of product supply interruptions and molecule-specific deactivations may have a significant and positive impact on the incidence rate and the duration of drug shortages over time.

The historical U.S. manufacturers of Doxil and methotrexate, like the manufacturers of other cancer drugs, generate revenue from reducing costs and making drugs that have the highest revenue potential. Therefore, we should expect firms to shift away from manufacturing older drugs with limited demand to higher revenue-producing drugs over time.

These reporting polices act as a “stick” to compel manufacturers to notify public agencies of their plans to reduce production and/or retire lines of drug production. They also may increase regulatory oversight of the quality of contract manufacturers, such as Ben Venue.

These policies complement the “carrot” offered by FDA to domestic firms to reduce the short-term costs of producing these drugs through the expedited review of ANDAs and clearance of existing supply lots by the FDA. It is important for the FDA to ensure the privacy of firms in meeting these reporting requirements, lest public policy unintentionally facilitate the firms’ collective monitoring of total supply.

Maintaining competition in these and related drug
markets is an important policy goal, since competition aids the adequate supply and quality of medically necessary drugs at non-monopoly (read, “low”) prices.

Yet, one aspect of these policies that was not adequately addressed by the FDA’s announcement is the system for distributing increases in the supply of Lipodox and preservative-free methotrexate to U.S. hospitals and provider groups.

Not all parts of the country or all providers are equally affected by these specific drug shortages, even though reports of them are widespread. It is likely that small, community, low-volume oncology practices may be the most vulnerable to interruptions in these products’ supply—and the most in need of increased access to these drugs.

Furthermore, pricing guidelines for the manufacturer of imported Lipodox and APP’s preservative-free methotrexate are not provided by the FDA’s announcement.

Economics 101 suggests manufacturers of medically necessary drugs in scarce supply should be able to command a high price from purchasers. It remains to be seen whether Sun Pharma and APP will set the prices of these products above historically observed market prices for these drugs.

Clarity is also needed regarding whether manufacturers will be able to set the prices of these drugs based on purchasers’ volume, or other indicators of willingness to pay (so-called “price discrimination”).

If price-discrimination is practiced by these firms, purchasers facing low prices for Doxil in particular may attempt to horde supply in anticipation that prices may go up again if supplies dwindle.

Again, it is likely that low-volume, community oncology practices remain vulnerable to hording and/or price gouging if the market is left to clear on its own.

Finally, the FDA also endorsed legislation that would provide user fee funding for the FDA to manage the drug shortages. User fees should be understood as a “tax” placed on the industry. It is likely these fees will be passed on to consumers in the form of higher prices.

While user fees may act as an additional incentive for manufacturers to incorporate redundancies and contingency planning into their production planning, there is no requirement that they do so in the policy outlined by the FDA.

Rena Conti is a health economist in the University of Chicago Section of Hematology/Oncology and Department of Pediatrics, and is a faculty affiliate at the University of Chicago Comprehensive Cancer Center.

Selected References for Further Reading

The Duke Scandal
S.C. Practice: Potti was Hired Based on Duke Recommendations
(Continued from page 1)

The practice has been under siege by local media after the 60 Minutes report that aired Feb. 12. The segment reported that after causing a debacle at Duke, where he is accused of having falsified both data and credentials, Potti obtained a South Carolina license and landed in Myrtle Beach.

The segment showed Potti’s name on the sign of the practice’s satellite office in the town of Loris.

Initially, the practice’s founder claimed to be unaware of the details that were presented in the 60 Minutes report “Deception at Duke.”

“We had no idea 60 Minutes was going to do this,” said Coastal Cancer Center’s Lawrence Holt to a publication called SCNow. “It caught us out of the blue.”

Many of the same details that made it into the 60 Minutes piece had previously appeared in The Cancer Letter, as well as in a variety of high-profile news organizations worldwide, including The Economist and on the front page of The New York Times.

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Now, after relentless publicity, the practice and the physician have ended their association. In a carefully worded press release, the Coastal Cancer Center avoided using the words “resigned” or “fired,” and instead pointed to Potti’s former Duke colleagues, who had given him glowing letters of recommendation. The letters were a “key factor” in Potti’s hiring.

Potti’s former Duke colleagues did indeed write glowing letters of recommendation to the South Carolina license board. One such letter was penned by Jeffrey Crawford, the George Barth Geller Professor for Research in Cancer and chief of medical oncology at Duke. Crawford addressed his letter to Holt, but the recommendation ended up in Potti’s application file at the licensure board.

“His clinical skills are excellent,” Crawford wrote in the letter dated Jan. 7, 2011. “During his tenure at Duke, Anil developed an impressive research program and helped the careers of a number of our fellows and junior faculty. He was always willing to help others around him and was an ideal model ‘team player.’ Despite a very active research program, Anil maintained his dedication to patient care and this always came first for him.”

Afterward, Crawford said he regrets writing the letter. “In retrospect, I realize that it was a mistake to send this letter without understanding the situation as I do today,” Crawford said in an email to The Cancer Letter (The Cancer Letter, Dec. 9, 2011).

Though Duke continues to claim that no patient was harmed in three clinical trials that tested Potti’s scientific findings, the institution did settle 11 malpractice claims filed by former patients, and is in the midst of fighting two lawsuits stemming from Potti’s work.

Meanwhile, the world’s premier medical journals have retracted Potti’s papers.

Papers based on Potti’s data have been retracted in The New England Journal of Medicine, Nature Medicine, The Lancet Oncology, PLoS ONE and Blood. The Journal of Clinical Oncology has retracted two papers. The most recent retraction was published by Clinical Cancer Research earlier this week: http://bit.ly/yO2TKS

The text of the press release by Potti’s former employer follows:

Dr. Anil Potti, MD is no longer associated with Coastal Cancer Center of Myrtle Beach, S.C. Dr. Potti, who saw patients primarily at Coastal Cancer Center’s Loris, S.C. and Brunswick County, N.C. facilities, served his final day on Feb. 21st. Potti originally joined Coastal Cancer Center as an oncologist in March 2011.

“A recent 60 Minutes story concerning an investigation of Duke University’s cancer research programs and Dr. Potti’s work there prompted many concerned people to contact Coastal Cancer Center with comments and questions,” said Lawrence B. Holt, Jr., MD, FACP, President of Coastal Cancer Center. “It has become obvious that this issue is going to take precious focus away from patient care. Coastal Cancer Center is staffed by incredibly caring people who want and need to concentrate on providing outstanding patient care.”

Coastal Cancer Center conducted a deep and thorough investigation of Potti’s credentials before hiring him. Potti received numerous letters of strong recommendation from key members of the medical community at Duke University where Potti had worked before coming to the Grand Strand.

“We received glowing references about Dr. Potti’s character and skills from the highest ranks of the Duke University School of Medicine and Duke University Medical Center,” said Holt. “We were assured by Duke Medical’s leaders that Anil was ‘outstanding in all categories,’ ‘had excellent clinical skills’ and that he had conducted himself at Duke with ‘honesty, integrity and humility.’ One Duke University director even went so far as to say he would be pleased to have Dr. Potti as the treating physician ‘if my own family had unfortunately contracted a cancer.’

Letters of recommendation came in from the chief of Duke Medical’s Division of Medical Oncology, the Chair of the Department of Medicine, the Director of Hematologic Malignancies Program, and several professors.

“During the time that Dr. Potti has been with us,” continued Holt, “he has been an exemplary physician whose caring ways have made him extremely popular with patients. We will miss him.”

During his time on staff at Coastal Cancer Center, Dr. Potti became an active part of the Grand Strand medical community, many of whom have reached out to him in the days since the 60 Minutes story aired.

“We have been touched and heartened by the outpouring of support for Anil that has come from the local medical community,” says Holt. “Like those of us at the Cancer Center, other physicians recognize him as an exceptional doctor and colleague.”

Dr. Holt and other Coastal Cancer Center physicians will personally assume the care of Dr. Potti’s patients.
Chemotherapy Drug Shortages in the United States: Genesis and Potential Solutions

Michael P. Link, Stanford University School of Medicine, Stanford, CA
Karen Hagerty, American Society of Clinical Oncology, Alexandria, VA
Hagop M. Kantarjian, MD Anderson Cancer Center, Houston, TX

In October 2011, the US Food and Drug Administration (FDA) announced the end of the cytarabine shortage. Cytarabine is the key chemotherapy drug for the management of leukemia in children and adults, particularly acute myeloid leukemia, and the announcement by the FDA of an end to this 11-month crisis was good news. However, in July 2011, we started experiencing shortages of daunorubicin, another drug critical to the management of leukemia and the second most important drug used to treat acute myeloid leukemia. The daunorubicin shortage has been mitigated somewhat by the fact that it can be replaced with other anthracyclines, albeit with different toxicity profiles. However, daunorubicin is an essential component of clinical trial protocols for leukemia in the United States, and its shortage has created serious challenges in conducting leukemia research.

Cytarabine Shortages: The Trigger for Heightened Awareness

First noted in December 2010, the cytarabine shortage entered public consciousness this spring with several reports in mainstream media about increasing shortages of chemotherapy drugs and their impact on thousands of patients with cancer. Chemotherapy shortages have included, at various times, doxorubicin, cisplatin, paclitaxel, etoposide, mechlorethamine, daunorubicin, cytarabine, fluorouracil, leucovorin, and many others. The shortages are not unique to chemotherapy agents but occur across a broad range of medicines. Chemotherapy drug shortages are generally more critical because of the lack of equivalent alternatives for most agents. Shortages seem to be most sharply felt in the United States, but they are a global phenomenon that exists in varying degrees around the world. They have grown at an alarming rate in the past 2 to 3 years and have tripled in the past 5 years.1 Five years ago, there were 70 drugs in short supply. Today, there are hundreds—and the epidemic seems to be worsening.

In addition to print and broadcast stories over the past few months, this crisis has been brought into focus through work performed by the American Society of Clinical Oncology (ASCO) and others in the medical community. In July 2011, ASCO together with other concerned organizations hosted a briefing for senior congressional staff to raise awareness and explore potential solutions. In September 2011, Charles Penley, MD, chair elect of the ASCO Government Relations Council, testified before the House Energy and Commerce Committee. ASCO has attended FDA meetings on the issue and offered preliminary recommendations on potential mechanisms for mitigating drug shortages. In November 2011, President Obama issued an executive order calling for the FDA to broaden reporting of potential drug shortages, hasten or facilitate the review process to more effectively prevent or respond to shortages, and work with the Department of Justice in cases of possible drug price gouging or stockpiling. This is a step in the right direction, but we should consider other approaches as well.

Contamination and Shortages of Raw Materials and Plant Shutdowns

To address the issue effectively, the root causes of the shortages should be identified. Among the numerous excellent articles published, four describe markedly different causes for the shortages (Table 1).2-5 Drug companies have pointed to contamination of and shortages in the supply of raw materials and shutdowns of plants by the FDA for quality control issues.6 In particular, according to the FDA, manufacturing and quality issues account for more than 50% of shortages, with shortages of active pharmaceutical ingredients accounting for only 5% to 10% of the problem.2-4 As the crisis has escalated, other causes have been highlighted. In Congressional hearings, representatives of generic drug companies have pointed to FDA regulatory complexities and burdensome administrative requirements to recertify manufacturing of generic drugs. Others have cited consolidation within the pharmaceutical industry, resulting in fewer companies willing to produce generic drugs.

Table 1. Cited Reasons for Chemotherapy Drug Shortages

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<th>Reason</th>
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<tr>
<td>Increased national and worldwide demand for oncology drugs</td>
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<tr>
<td>Shortages of supply of raw materials</td>
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<tr>
<td>Production problems; contamination of materials</td>
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<tr>
<td>Aging production plants</td>
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<tr>
<td>Limited inventories of generic drugs to reduce company costs</td>
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<tr>
<td>Limited profit margins for generic drugs; Medicare ASP + 6% reimbursement system</td>
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<td>Gray market, stockpiling, and price gouging</td>
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<tr>
<td>Private oncologists favoring use of name brand over generic drugs</td>
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<td>FDA over-regulation and long timelines to approve new sources of generic drugs</td>
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Abbreviations: ASP, average sales price; FDA, US Food and Drug Administration.
Market Dynamics

We believe that the unifying mechanism behind the drug shortage can be traced to simple economics. Manufacturers have little incentive to produce drugs with low profit margins and often shift their resources to drugs for which higher profit margins can be anticipated. The vast majority of chemotherapy drug shortages have been in sterile injectable generic agents, most of which are relatively inexpensive to purchase. As described by Chabner,5 there are a few drug companies (eg, Teva Pharmaceuticals [Petah Tikva, Israel], Bedford Laboratories [Bedford, OH], APP Pharmaceuticals [Schaumburg, IL], Hospira [Lake Forest, IL]) that account for more than 70% of the generic chemotherapy market. With aging plant facilities and limited financial incentives, a breakdown in one manufacturing component might shift the interests and resources of a company to more lucrative products, precipitating a drug shortage. It has been suggested that because of higher profit margins in non-US markets, it is possible some generic drugs are being diverted to foreign markets, thus exacerbating the problem.5

Medicare Reimbursement System

Established by the Medicare Modernization Act of 2003, the Medicare formula for reimbursement of physician-administered drugs under Part B was designed to control the rapidly escalating cost of chemotherapy drugs.7,8 Simply stated, Medicare caps at 6% the amount over the average sales price (ASP) that it will reimburse physicians for drugs used in their practices. Because of the methodology used by Medicare to calculate the ASP, there is a 6-month lag between the time the manufacturers submit their ASP data and when changes in sales prices are reflected in reimbursement. This has the practical effect of making it difficult for manufacturers to raise their prices more than 6% in any 6-month period (because raising the price more than that would cause reimbursement for the drug to be less than the actual selling price) and leaves little flexibility for prices to adapt to free-market supply and demand. The Medicare Modernization Act was implemented in 2005; shortages in chemotherapy drugs began to escalate within a year and have increased dramatically since 2008.

As in most normally functioning free markets, competition among sellers—in this case, generic manufacturers—leads to a decrease in prices. In the case of shortages, the market would be expected to respond with increasing prices. But with regard to chemotherapy, the Medicare payment system has made it difficult to raise prices, creating a situation in which—for low-cost drugs with dwindling profit margins—there is little incentive for continued production. Although a recent report from the Assistant Secretary for Planning and Evaluation of the US Department of Health and Human Services10 examining part of this issue did not explicitly conclude that ASP plus 6% was a driving force in shortages, it clearly stated that drugs that have not been in shortage had stable or increasing prices during the period under study, whereas drugs that have gone into shortage almost universally witnessed their prices decrease before the shortage period. Thus, it is possible that the well-intended Medicare rule has had unfortunate and unexpected longer-term consequences that have contributed to the current situation.

In Europe, where there is no such Medicare rule, the prices of generic drugs are higher than in the United States, and the prices of brand drugs are lower (because of agreements between drug companies and governments). This maintains a reasonable profit margin for generic drugs, allowing competition to continue and largely preventing drug shortages.

Gray Market

The shortages have created an opportunity for secondary drug distributors to make additional profits. With early knowledge of potential drug shortages, they have hoarded chemotherapy drugs in anticipation and sold them at amounts 650% to 3,000% of the original prices.10 This activity is referred to as constituting a gray market and is actually a form of price gouging. The gray market has raised additional concerns about the reliability of drugs being sold to practices, because the pedigree of the drugs is uncertain. There is limited to no ability to trace their chain of custody, nor can we be assured that they have been handled, stored, and transported as required. It is estimated that the gray market accounts for up to 50% of drug sales during a drug shortage.4

Financial Pressure Experienced by Oncologists

In a recent opinion piece published in the New England Journal of Medicine, Gatesman et al4 argue that because Medicare still reimburses oncologists under a buy-and-bill system, there is incentive for oncologists to select higher-priced alternatives as a means for increasing profits. They suggest that faced with the choice of two equally effective drugs—a low-cost generic or higher-cost brand drug—oncologists might choose the latter to increase the margin provided by the Medicare 6% markup, thereby creating a disincentive for the pharmaceutical industry to manufacture generic drugs. We feel that this argument is overly simplistic and does not fully appreciate the complexities of the issue. The fact is that most shortages are occurring in drugs used for diseases for which there is no real treatment alternative (in other words, the oncologist often has no viable alternative to the generic drug). Furthermore, it is important to remember that the intent of the average wholesale price and ASP plus 6% was to allow oncologists to make profits on chemotherapy injectable drugs to cover the practice costs of infusion centers, which are not reimbursed otherwise. This strategy aimed to shift patients out of expensive hospital-based infusion centers and into less expensive practice settings that were also closer to patients’ homes and thus more convenient. Overall, the private oncology arm of cancer therapy has been a highly successful endeavor in delivering optimal cancer care in the United States. Reducing the drug margin significantly may lead to a reverse trend (ie, private oncology practices shutting down and/or joining academic or hospital-based practices). This may ultimately reduce access to cancer care in smaller towns and rural areas. It will also discourage current trainees from specializing in medical oncology, thus shrinking the pool of specialists and consequently reducing the quality of cancer care delivery in the United States.

Possible Solutions

Establishment of a pricing floor for generic chemotherapy drugs. The average price of 1 g of cytarabine is $12 to $16. The average price of a vial of carboplatin is less than $5. Under the Medicare reimbursement system, limitations on price increases may mean certain generic drugs will never be profitable enough from a manufacturing perspective. One alternative would be to set a minimum price for generics based on some comparison with a similar brand drug. For example, if a brand drug costs $50,000 per year, the generic drug may be priced at 5% to 10%, or $2,000 to $5,000 per
year. This could provide sufficient incentive for generic drug companies to remain in, or enter, the market.

**Mandatory reporting.** Legislation introduced by Senators Amy Klobuchar and Bob Casey, and supported by President Obama via executive order, would require that manufacturers provide the FDA with 6 months notice of anticipated drug shortages. Some have worried that this would exacerbate hoarding, either on the part of distributors in preparation for price gouging or hospitals and practices wanting to maintain adequate supply. However, much of the communication that would be mandated would be confidential, allowing the FDA to take steps to mitigate problems without necessarily publicizing this information. Since the issue of drug shortages has gained national attention, the FDA has been the beneficiary of more proactive reporting of shortages and potential shortages from the manufacturers. In 2011, this allowed the FDA to prevent more than double the number of shortages it prevented in 2010. Some have proposed adding a provision to pending legislation requiring manufacturers and/or the FDA to locate alternative supplies within 3 to 6 months of notification of a pending shortage. We think this is worth consideration.

**Review of FDA timelines.** There is reportedly a backlog of more than 2,000 unapproved generic applications, with a median time to approval of 30 months. It is imperative that the FDA allocate the resources needed to significantly decrease this timeline to approval, thus allowing more entrants into the generic market within the 6-month timeline of the anticipated drug shortage. Apart from the obvious benefit of more timely supply to the market of needed life-saving drugs, the production of adequate capacity would significantly reduce the presence of gray-market players.

**Conclusion**

There are numerous causes for the escalating drug shortage crisis, but in our view, none are as powerful as simple economics. The most straightforward solution is to change the way generic sterile injectables are reimbursed. As suggested earlier, if the generic drug price is kept at 5% to 10% of the brand drug price, and/or the ASP plus 6% reimbursement is modified to an ASP plus 10% to 20%, the profit margin will remain reasonable, and generic drug companies will have adequate incentive to continue to supply the drug. There may be other approaches to financial incentives that would achieve the same end, and such suggestions would be welcome. Although some experts worry about increasing the cost of care, it should be noted that: first, increasing generic drug prices, which account for 2% of the total cost of chemotherapy drugs, will have a minimal effect on the total cost of cancer care; second, the continuing drug shortages may be costing as much as $200 to $300 million per year; third, money can be saved if oncologists have access to reasonably priced generic drugs; fourth, increased costs attributable to the gray market will be eliminated; and fifth, medical errors caused by changing to untested practices will be reduced.

This simple modification in the Medicare rule would hopefully resolve many of the downstream issues. We draw special attention to the gray market and price gouging. These should be investigated at both the state and national levels, and consideration should be given to making these activities explicitly illegal. Finally, the Obama administration should redouble its efforts to streamline regulatory processes so that new applications for generic drugs can complete FDA review within 3 to 6 months of an announced or impending drug shortage. In terms of American lives, a solution to the problem is priceless.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** None Consultant or Advisory Role: None Stock Ownership: None Honoraria: None Research Funding: Michael P. Link, Seattle Genetics, Pfizer

**Expert Testimony:** None Other Remuneration: None

**AUTHOR CONTRIBUTIONS**

Manuscript writing: All authors
Final approval of manuscript: All authors

**REFERENCES**


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Bill Summary & Status
112th Congress (2011 - 2012)
H.R.2245
CRS Summary

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H.R.2245
Latest Title: Preserving Access to Life-Saving Medications Act of 2011

SUMMARY AS OF:

Preserving Access to Life-Saving Medications Act of 2011 - Amends the Federal Food, Drug, and Cosmetic Act to require the manufacturer of a prescription drug marketed in interstate commerce to notify the Secretary of Health and Human Services (HHS) of a discontinuance or interruption in the manufacture of such drug. Requires the notification to be submitted six months prior to the date of a discontinuance or interruption, if possible.

Allows the reduction of the notification period if the manufacturer certifies to the Secretary that good cause exists for the reduction. Authorizes the Secretary to reduce the notification period based on the type of discontinuance or interruption at issue or any other factor.

Treats any information provided to the Secretary under this Act as a trade secret or confidential information.

Establishes civil monetary penalties for violations.

Requires the Secretary to publish on the website of the Food and Drug Administration (FDA) and distribute to the appropriate health care providers and patient organizations information on discontinuances, interruptions, and drug shortages.

Requires the Secretary to notify a manufacturer of: (1) any determination by the Secretary that a drug may be vulnerable to a drug shortage, and (2) the Secretary’s duty to collaborate to improve continuity of supply. Prohibits the Secretary from requiring a manufacturer to: (1) manufacture a drug in the event of a discontinuance or interruption, or (2) delay or alter a discontinuance or interruption.
Declares that no provision of federal law shall be construed to prohibit a manufacturer from, or penalize a manufacturer for, allocating distribution of its products in order to manage an actual or potential drug shortage.

Requires the Comptroller General to examine issues related to drug shortages.
Bill Summary & Status
112th Congress (2011 - 2012)
S.296
CRS Summary

Item 3 of 3

S.296
Latest Title: Preserving Access to Life-Saving Medications Act
Latest Major Action: 2/7/2011 Referred to Senate committee. Status: Read twice and referred to the Committee on Health, Education, Labor, and Pensions.

SUMMARY AS OF:
2/7/2011--Introduced.

Preserving Access to Life-Saving Medications Act - Amends the Federal Food, Drug, and Cosmetic Act to require a prescription drug manufacturer to notify the Secretary of Health and Human Services (HHS) of a discontinuance, interruption, or other adjustment of the manufacture of the drug that would likely result in a shortage of such drug. Requires: (1) six months notice of any discontinuance or planned interruption or adjustment, and (2) notice as soon as practicable after becoming aware of such interruption or adjustment in the case of any other interruption or adjustment. Applies this Act to any approved prescription drug that is not a product that was originally derived from human tissue and was replaced by a recombinant product.

Sets forth the types of adjustment for which a manufacturer must submit notice, including: (1) adjustments related to the supply of raw materials, (2) adjustments to production capabilities, (3) business decisions that may affect the manufacture of the drug, and (4) other adjustments as determined appropriate by the Secretary.
HR 3839 IH

112th CONGRESS

2d Session

H. R. 3839

To address critical drug shortages.

IN THE HOUSE OF REPRESENTATIVES

January 31, 2012

Mr. CARNEY (for himself and Mr. BUCSHON) introduced the following bill; which was referred to the Committee on Energy and Commerce, and in addition to the Committee on the Judiciary, for a period to be subsequently determined by the Speaker, in each case for consideration of such provisions as fall within the jurisdiction of the committee concerned

A BILL

To address critical drug shortages.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the `Drug Shortage Prevention Act of 2012'.

SEC. 2. TABLE OF CONTENTS.

The table of contents of this Act is as follows:

Sec. 1. Short title.

Sec. 2. Table of contents.

Sec. 3. Actions by Food and Drug Administration To Address Critical Drug Shortages.

Sec. 4. Actions by Attorney General To Address Critical Drug Shortages.
SEC. 3. ACTIONS BY FOOD AND DRUG ADMINISTRATION TO ADDRESS CRITICAL DRUG SHORTAGES.

Chapter V of the Federal Food, Drug, and Cosmetic Act is amended by inserting after section 506C (21 U.S.C. 356c) the following:

`SEC. 506D. ADDRESSING CRITICAL DRUG SHORTAGES.

` (a) Definitions- In this section:

` (1) The term `biological product' has the meaning given to such term in section 351(i) of the Public Health Service Act.

` (2) The term `critical drug' has the meaning given to such term by the Secretary pursuant to subsection (b)(2).

` (3) The term `critical drug shortage' has the meaning given to such term by the Secretary pursuant to subsection (c)(2).

` (4) The term `relevant stakeholders' includes--

` (A) with respect to drugs and biological products, manufacturers, distributors, and group purchasing organizations; and

` (B) health care providers.

` (b) National Critical Drug List-

` (1) LIST- The Secretary shall--

` (A) not later than 180 days after the date of the enactment of this section, establish a list identifying each critical drug;

` (B) promptly remove any drug or biological product from such list if the drug or biological product no longer meets the definition of a critical drug established pursuant to paragraph (2);

` (C) consider for inclusion in such list--

` (i) each drug and biological product that is--

` (I) approved or licensed under section 505 of this Act or section 351 of the Public Health Service Act; or

` (II) otherwise marketed pursuant to regulation by the Food and Drug Administration; and

` (ii) each such drug or biological product for which a new indication is approved;
(D) include in such list, with respect to each listed critical drug, information concerning the number and identity of the manufacturers of such drug;

(E) make such list publicly available; and

(F) review and update such list semiannually.

(2) DEFINITION- Not later than 90 days after the date of the enactment of this section, the Secretary shall define the term `critical drug' for purposes of this section. In defining such term, the Secretary shall--

(A) solicit input from relevant stakeholders through a public hearing or an opportunity to provide written comments;

(B) take into account the medical necessity of a drug or biological product and exclude any drug or biological product that is not medically necessary; and

(C) take into account the vulnerability of a drug or biological product to shortage, including because of the number of manufacturers and sources of active ingredients involved.

(3) REQUEST FOR REMOVAL-

(A) IN GENERAL- The manufacturer of a drug or biological product on the list established under paragraph (1) may request that the Secretary remove the drug or biological product from the list on the basis that the drug or biological product does not satisfy the definition of a critical drug.

(B) ACTION BY THE SECRETARY- Not later than 45 days after receipt of such a request, the Secretary shall review the determination that the drug or biological product is a critical drug and--

(i) remove the drug or biological product from the list established under paragraph (1) if the Secretary determines that the drug is not a critical drug; or

(ii) provide to the manufacturer submitting such request an explanation of why the drug or biological product was properly determined to be a critical drug.

(c) National Critical Drug Shortage List-

(1) LIST- The Secretary shall--
(A) not later than 1 year after the date of the enactment of this section, establish and make publicly available a list identifying each critical drug that is in a critical drug shortage; and

(B) not less than monthly, review and, as appropriate, update such list.

(2) DEFINITION- Not later than 180 days after the date of the enactment of this section, the Secretary shall define the term `critical drug shortage' for purposes of this section. In defining such term, the Secretary shall--

(A) solicit input from relevant stakeholders through a public hearing or an opportunity to provide written comments; and

(B) limit the definition to actual shortages in the United States of critical drugs.

(3) CONTENTS- The list established under paragraph (1) shall, with respect to each listed critical drug shortage, include at a minimum access to the following information:

(A) Indication of the severity of the shortage.

(B) Each reason for the shortage.

(C) An estimated date by which the critical drug involved will begin reaching providers in quantities sufficient to meet demand.

(D) Identification of alternate therapies.

(E) Identification of specific regions of the country particularly affected or specifically not affected by the shortage.

(4) REQUEST FOR REMOVAL-

(A) IN GENERAL- The manufacturer of a critical drug included on the list established under paragraph (1) may request that the Secretary remove the critical drug from the list on the basis that the drug is not in a critical drug shortage.

(B) ACTION BY THE SECRETARY- Not later than 45 days after receipt of such a request, the Secretary shall review the determination that a critical drug shortage exists and--

(i) remove the critical drug from the list if the Secretary determines that the drug is not in a critical drug shortage; or
(ii) provide to the manufacturer submitting such request an explanation of why the critical drug was properly determined to be in a critical drug shortage.

(d) Supply Chain Communication Infrastructure-

(1) NOTIFICATIONS TO PUBLIC-

(A) IN GENERAL- The Secretary shall establish and implement a proactive system for giving notice to the public concerning additions and other modifications to the list under subsection (c)(1) regarding critical drug shortages.

(B) SYSTEM REQUIREMENTS- The system under subparagraph (A) shall provide such notices--

(i) to any member of the public on an opt-in basis; and

(ii) in written form comprehensible to a lay reader.

(C) INITIAL IMPLEMENTATION- The Secretary shall begin implementation of the system under subparagraph (A) not later than 1 year after the date of the enactment of this section.

(2) NOTIFICATIONS TO MANUFACTURERS AND DISTRIBUTORS-

(A) IN GENERAL- The Secretary shall establish and implement a system for giving notice of any imminent critical drug shortage to--

(i) any manufacturer of the critical drug registered under section 510;

(ii) any manufacturer so registered with capacity to manufacture the critical drug or an alternate therapy to the critical drug; and

(iii) subject to subparagraph (B) and at the Secretary's discretion, any wholesale distributor of the critical drug that has a contractual relationship with--

(I) the manufacturer of the critical drug; or

(II) an authorized distributor of record (as such term is defined in section 503(e)(3)) of the critical drug.

(B) WHOLESALE DISTRIBUTORS PARTICIPATING IN UNLAWFUL ACTIVITIES- If the Attorney General determines that a wholesale distributor of a critical drug is participating in stockpiling, price gouging, or other unlawful activities related to the distribution of a
critical drug, the Secretary shall withhold any notification that would otherwise be made to the distributor under subparagraph (A) with respect to the critical drug until the Attorney General determines that the distributor is no longer participating in such activities.

`(C) INITIAL IMPLEMENTATION- The Secretary shall begin implementation of the system under subparagraph (A) not later than 180 days after the date of the enactment of this section.

`(3) NOTIFICATIONS TO ATTORNEY GENERAL- The Secretary shall--

`(A) give notice to the Attorney General of any critical drug shortage listed under subsection (c); and

`(B) provide such information to the Attorney General as may be necessary to determine the extent to which it is appropriate to increase one or more production quotas under section 306(h) of the Controlled Substances Act in order to address such shortage.

`(e) Study on Feasibility of National Contingency Plan-

`(1) STUDY- The Secretary shall conduct a study on the feasibility of creating a national contingency plan addressing critical drug shortages, including with respect to--

`(A) the creation of a Federal stockpile of critical drugs for the purpose of responding to potential critical drug shortages; or

`(B) the expansion of an existing Federal stockpile of drugs to include critical drugs for such purpose.

`(2) CONSULTATION- In conducting the study under paragraph (1), the Secretary shall consult with relevant stakeholders.

`(3) REPORT- Not later than 1 year after the date of the enactment of this Act, the Secretary shall complete the study required by paragraph (1) and submit to the Congress a report on the results of such study.

`(f) Approval of Drugs-

`(1) EXPEDITED REVIEW- The Secretary shall expedite the review of--

`(A) any application seeking approval of a critical drug under subsection (c) or (j) of section 505 of this Act or licensing of a critical drug under section 351 of the Public Health Service Act; and

`(B) any request by the sponsor of a critical drug to approve--
(i) a change to the manufacturing process for a critical drug, including any change in the facilities used for such process; or

(ii) an alternate supplier of any active ingredient in a critical drug.

(2) NO DELAY OF OTHER APPLICATIONS- In expediting the review of applications and requests under paragraph (1), the Secretary shall not unnecessarily delay the review of applications and requests for drugs and biological products that are not critical drugs.

(3) ESTABLISHMENT OF PROCEDURES AND TIMEFRAMES- Not later than 90 days after the date of the enactment of this section, the Secretary, with input from relevant stakeholders, shall establish procedures and timeframes for providing expedited review under paragraph (1).

(g) Improved Regulation- The Secretary shall review and improve the process for regulating critical drugs so as to--

(1) ensure that, at each stage of such process, the status of such drugs as critical drugs is taken into consideration;

(2) improve communications between the offices and officials of the Food and Drug Administration responsible for approving and regulating critical drugs and the offices and officials of the Food and Drug Administration responsible for identifying and addressing critical drug shortages; and

(3) ensure that any new regulatory concern about a critical drug identified by Food and Drug Administration personnel is communicated--

(A) within 1 business day to the office of the Food and Drug Administration responsible for identifying and addressing critical drug shortages; and

(B) within 5 business days to the manufacturer of the critical drug.

(h) Confidentiality-

(1) IN GENERAL- Except as described in paragraph (2), in carrying out this section, the Secretary shall not disclose--

(A) any trade secret or other matter that is referred to in section 1905 of title 18 of the United States Code, or

(B) any trade secret or other commercial or financial information that is exempt from disclosure under section 552(b)(4) of title 5 of the United States Code.
(2) DISCLOSURE TO FEDERAL OFFICERS AND EMPLOYEES- The Secretary may disclose such matter or information to an officer or employee of the Federal Government, but only if--

(A) such disclosure is for the purpose of carrying out this section or section 306(h) of the Controlled Substances Act; and

(B) any further disclosure of such matter or information by the officer and employee is restricted to the same extent as disclosure of such matter or information by the Secretary.

(i) Sense of Congress Regarding Increase in Personnel- It is the sense of the Congress that the Food and Drug Administration should increase the number of personnel responsible for identifying and addressing critical drug shortages.'.

SEC. 4. ACTIONS BY ATTORNEY GENERAL TO ADDRESS CRITICAL DRUG SHORTAGES.

Section 306 of the Controlled Substances Act (21 U.S.C. 826) is amended by adding at the end the following:

(h) If the Secretary of Health and Human Services lists a critical drug shortage under section 506D(c) of the Federal Food, Drug, and Cosmetic Act, and the drug involved or any ingredient therein is a controlled substance subject to a quota under this section, then the Attorney General shall increase such quota to the extent determined by the Attorney General, in consultation with the Secretary of Health and Human Services, to be appropriate to address the critical drug shortage.'.