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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.[i] 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.[ii] [iii] 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.[iv] [v] 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).[vi]

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.[vii]

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).[viii] Shortages of drugs have triggered clinical mistakes and bad outcomes in situations where patients received medicines that prescribers weren't accustomed to using.[ix] 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.[x] 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.[xi]

In the case of propofol, the FDA allowed another version of the drug to be imported temporarily.[xii] 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.[xiii]

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 levofolinate, 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. Levofolinate 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.[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.[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.[xvi] [xvii]

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.[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.[xx] 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.[xxi]

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.[xxii]

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.[xxiii] 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.[xxiv]

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

We should consider policy constructs that would give manufacturers a financial incentive to develop intellectual property that improved the manufacturing characteristics of generic medicines even if these changes it didn't 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.[xxvi]

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.[xxx] 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,[xxxi] 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. [xxxii] 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.[xxxiii] 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.

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[i] UK Lawmakers to Probe Medicine Shortages. Reuters, November 21, 2011.

[ii] Laura Eggertson. Continuing drug shortages affect North American patients. Canadian Medical Association. Journal 2010;18:E811

[iii] 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.

[iv] Food and Drug Administration. Current drug shortages (http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050792.htm)

[v] Kaakeh R, Sweet BV, Reilly C, et al. Impact of drug shortages on U.S. health systems. Am J Health Syst Pharm 2011;68:1811-9.

[vi] Drug Shortages: A closer look at products, suppliers, and volume volatility. IMS Institute for Healthcare Informatics, November 2011.

[vii] Drug Shortages: A closer look at products, suppliers, and volume volatility. IMS Institute for Healthcare Informatics, November 2011.

[viii] Drug Shortages: A closer look at products, suppliers, and volume volatility. IMS Institute for Healthcare Informatics, November 2011.

[ix] Provisional observations on drug product shortages: Effects, causes, and potential solutions. Summary of a stakeholder's meeting on drug shortages convened by the American Medical Association and the American Society of Health-System Pharmacists. American Journal of Health-System Pharmacists 2002;59:173-182.

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[xvi] Kaakeh R, Sweet BV, Reilly C, Bush C, DeLoach S, Higgins B, Clark AM, Stevenson J. Impact of drug shortages on U.S. health systems. American Journal of Health System Pharmacists October 2011;68(19):1811-9.

[xvii] Drug shortages cost U.S. care providers at least $200 million annually, pose patient safety risks, research suggests. Charlotte, N.C: Premier, Inc; Mar 28, 2011. Available at: www.premierinc.com/about/news/11-mar/drugshortage032811.jsp

[xviii] 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.

[xix] Scott Gottlieb. Solving the growing drug shortages. The Wall Street Journal, November 07, 2011. A21 available at http://www.aei.org/article/health/healthcare-reform/solving-the-growing-drug-shortages/

[xx] 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.

[xxi] 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.

[xxii] 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.

[xxiii] To Precent Drug Shortages, Don't Look to Inspections, FDA Says. The Pink Sheet Daily, August 22, 2011

[xxiv] 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.
[xxv] 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.
[xxvi] Valerie Jensen and Bob A. Rappaport. The Reality of Drug Shortages — The Case of the Injectable Agent Propofol. New England Journal of Medicine 2010; 363:806-807.
[xxvii] Kuehn BM. Influenza vaccine makers seek ways to speed production, boost effectiveness. Journal of the American Medical Association 2011;305(11):1079-80.
[xxviii] Wynn Bailey. Globalization of the Life Sciences Supply Chain. Contract Pharma, January/February 2011. (available at www.contractpharma.com)
[xxix] More than 80% of the raw materials used in pharmaceuticals come from outside the United States.
[xxx] Preserving Access to Life-Saving Medications Act (S.296)
[xxxi] Mandy L. Gatesman and Thomas J. Smith. The Shortage of Essential Chemotherapy Drugs in the United States. New England Journal of Medicine 2011;365;18
[xxxii] 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."
[xxxiii] 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 20910 was by 3 or fewer manufacturers.