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FDA's Contribution to the Drug Shortage Crisis

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Darrell Issa (CA-49), Chairman



FDA's Contribution to the Drug Shortage Crisis

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Executive Summary

American patients and doctors currently confront an unprecedented shortage of critical drugs. The widespread shortages are causing inferior treatment regimens, interruptions in care, higher health care costs, and even premature death. The drugs in shortage are mostly generic injectable medications, many of which have been on the market for decades. Although the shortages have been attributed to a myriad of factors from a lack of raw materials to increased demand, information obtained by the Committee on Oversight and Government Reform shows that the crisis was largely sparked by actions of the Food and Drug Administration (FDA). The Committee has learned that FDA regulatory activity has effectively shut down 30% of the total manufacturing capacity at four of America's largest producers of generic injectable medications: Bedford Laboratories, Hospira Pharmaceuticals, Sandoz Pharmaceuticals, and Teva Pharmaceuticals. Of the 219 drugs listed on the American Society of Health System Pharmacists (ASHSP) shortage list as of February 21, 2012, at least 128 – 58% of the drugs on the shortage list – were produced by at least one facility undergoing FDA remediation.

The drug shortage crisis that took off in 2010 began shortly after Margaret Hamburg became FDA Commissioner. Since this time, the FDA has failed to ensure that enforcement and compliance activities are conducted in a manner that does not create unnecessary shortages of critical drugs. In response to FDA prodding, companies producing generic injectable drugs have taken their manufacturing off-line simultaneous to other generic competitors also going off-line. These simultaneous shutdowns diminish the ability of competitors to alleviate the shortages with increased production. Last year, a report from the Assistant Secretary for Planning and Evaluation at HHS acknowledged the risk from shutting down manufacturing lines:

This temporary closure of a large manufacturing facility can also lead to other facilities being unable to meet the increased demand for the drug due to the lack of excess capacity and the pressure of ramping up supply for multiple drugs in other facilities.

Among shuttered manufacturing lines that occurred over the previous two years, the committee's review did not find any instances where the shutdown was associated with reports of drugs harming customers.

When problems that do not pose an immediate threat to public safety are detected, directing facilities to make targeted improvements under close supervision of the FDA can be a more appropriate response than actions that lead companies to shut down manufacturing lines. While such a response may place inconvenient burdens on the FDA's bureaucracy, greater use of such a targeted approach would have significantly diminished the public health crisis the country is facing from the abundant number of drug shortages. It is noteworthy, however, that the overall damage inflicted by the FDA's decisions to shutter manufacturing lines may extend well beyond the current drug shortage crisis. The shortages of generic injectable drugs are only the most visible result thus far of the FDA's stepped up enforcement activities.

While FDA actions over the past several years are the primary reason for the severity of the drug shortage crisis, the Committee also found that growing market concentration over the

past decade laid the groundwork for the crisis. One contributing factor to the growing market concentration is a provision of the Medicare Modernization Act (MMA) which dramatically reduced the prices paid by Medicare for many generic injectable medications, particularly older generics. Manufacturers are reluctant to raise prices above what Medicare reimburses providers who administer them. As a result, the Committee has learned that manufacturers are losing money producing generic injectable oncology drugs. When manufacturers lose money on a product, they are incentivized to switch production away from that product. Therefore, it is not surprising that many of the drugs on the shortage list are generic oncology drugs. A recent economics research paper found that drugs more affected by the MMA are much more likely to be in short supply than drugs less affected by the MMA.

Group purchasing organizations (GPOs) have also contributed to a market structure that makes shortages more likely. GPOs, which emerged as a mechanism for providers to increase their buying power, assemble large networks of hospitals and clinics who agree to purchase drugs through a GPO. GPO contracts, which are structured to take advantage of large economies of scale in drug production, result in only a few large manufacturers producing each generic injectable medication. Because of intense manufacturer competition to win GPO contracts, prices are driven down – the intended goal. As a consequence, however, companies that cannot produce a drug at large enough output levels to take advantage of the economies of scale – often because they lack the guaranteed source of demand that GPOs provide – will stop producing the drug or will neglect to enter the market.

Largely because of GPO contracting and the MMA's impact on changing Medicare's reimbursement formula for injectable medications, individual generic injectable drugs are being produced by at most three companies. In 2010, 90% of generic injectable oncology drugs were produced by three or fewer manufacturers. In such a tight oligopoly, the temporary closure of a significant number of the production lines in one or two manufacturers' facilities makes shortages much more likely.

Although the drug shortage crisis is likely to continue until manufacturers bring their facilities back on line, policymakers can take action to guard against future crises. Most importantly, a common sense regulatory approach must be restored at the FDA. Agency protocols should be revised so that the agency is required to consider the implications of its actions on the nation's supply of critical drugs. In addition, the drug shortage crisis has shed greater transparency on the dysfunctional price system that governs generic injectable medications. To improve the price mechanism, Congress should reform the way that Medicare pays for drugs so the program's reimbursements better reflect actual supply and demand conditions in the market. In the meantime, proposals to allow drug companies to share information about each other's manufacturing capability and product availability may have merit because of the extraordinary circumstances of the present crisis. However, this type of information sharing potentially places consumers at risk of collusion by the large manufacturers.

Key Findings:

- Information obtained by the Committee demonstrates the widespread shortages of generic injectable medications are due to two main factors. The first is growing market concentration over the past decade, which was accelerated by a provision in the Medicare Modernization Act (MMA). The second is increased FDA enforcement and regulation, which has shut down a substantial amount of manufacturing capacity.
- In 2009, Margaret Hamburg became FDA Commissioner. Between 2009 and 2010, the number of warning letters sent by the agency increased 42%. Between 2010 and 2011, the number of warning letters sent by the FDA increased an additional 156%. In many cases, warning letters have resulted in companies agreeing to take manufacturing off-line to address FDA criticisms.
- In response to FDA prodding, companies producing generic injectable drugs have taken their manufacturing off-line simultaneous to other generic competitors also going off-line. These simultaneous shut downs diminish the ability of competitors to offset shortages with increased production. Prior to these actions, Bedford Laboratories, Hospira Pharmaceuticals, Sandoz Pharmaceuticals, and Teva Pharmaceuticals were producing nearly one billion units of generic injectable products per year. Facilities at these companies are currently operating at about 700 million units per year, a 30% decrease in manufacturing capacity at America's primary production facilities for generic injectable drugs. This decrease is a massive reduction in the industries' capacity to supply the nation with injectable medications. The Committee could not find any evidence that any of the products produced at the facilities undergoing remediation had harmed anyone.
- Of the 219 drugs listed on the American Society of Health System Pharmacists (ASHSP) shortage list as of February 21, 2012, at least 128 – 58% of the drugs on the shortage list – were produced by at least one facility undergoing FDA remediation. Based upon the Committee's investigation, it is clear that over the past three years the FDA has failed to protect adequate drug supply in efforts to remedy manufacturer problems.
- The Medicare Modernization Act (MMA) changed the reimbursement rate for injectable drugs delivered in outpatient settings and capped the growth rate in Medicare's reimbursement paid to providers for administering these drugs. The impact of the MMA's pricing changes has been to dramatically reduce the price of older, generic drugs administered in non-hospital settings. For example, Carboplatin, Ondansetron, and Irinotecan, three chemotherapy drugs, experienced price declines of approximately 90% in just their first year off patent. The prices for these drugs have not risen despite each of them being in shortage.
- The Committee asked America's largest manufacturers of generic injectable medications whether they were losing money on oncology drugs, which tend to be administered in non-hospital settings. Most of the companies indicated they were producing several oncology drugs at a loss. For example, one company responded that it is producing about

three-quarters of its nearly two dozen oncology drugs at a loss. Significant capacity constraints and the negative margins also contribute to generic oncology drug shortages.

- The Medicare Modernization Act (MMA) had the large and negative unintended consequence of increasing concentration in the generic injectable drug market and reducing company incentives to invest in upgrading manufacturing capabilities for generic injectable drugs.

I. Extent of the Drug Shortage Crisis

Drug shortages can cause delays with patient treatment, interruptions in care, doctors using less preferred treatment regimens, and premature death. Drug shortages lead doctors to ration medicines, forcing them to judge who is most deserving of the needed drugs.¹ In extreme cases, doctors may be forced to decide who will live and who will die. Over 200 drugs, including 26 oncology drugs, appeared on the ASHSP drug shortage list as of February 21, 2012.² 80% of the drugs in shortage were generic injectable medications,³ and half of all generic injectable medications sold in the United States were on the shortage list as of February 21, 2012.⁴ Shortages of these drugs are not widespread features of other developed countries' health systems.⁵

The drug shortage crisis is a particular concern for the more than half-a-million cancer patients in the country.⁶ According to Dr. Michael Link, president of the American Society of Clinical Oncology, "If you are a pediatric oncologist, you know how to cure 70 to 80% of patients. But without these drugs you are out of business."⁷ Dr. Michelle Hudspeth, Division Director of Pediatric Hematology/Oncology at the Medical University of South Carolina, testified about the disturbing nature of the shortage problem at a November 2011 hearing of the Committee on Oversight and Government Reform Subcommittee on Health Care, District of Columbia, Census, and National Archives:

Regrettably, most institutions have had to institute a review board, often with involvement of their institutional ethics committee, to develop harrowing plans of how to ration chemotherapy drugs – most of which are generic drugs that have been around for 30 years or more. How do you decide who should be given the chance to live?⁸

Although much of the media attention has focused on the shortages of oncology drugs, the crisis is significantly broader. For example, about 90% of all the anesthesiologists in the country report they are experiencing a shortage of at least one anesthetic.⁹ Other specialists,

¹ Richard Knox, "Shortages Lead Doctors to Ration Critical Drugs," NPR News, October 3, 2011. Available at: <http://capsules.kaiserhealthnews.org/index.php/2011/10/shortages-lead-doctors-to-ration-critical-drugs/>.

² American Society of Health-System Pharmacists, "Drug Shortages: Current Drugs." Available at: <http://www.ashp.org/DrugShortages/Current/> (February 21, 2012).

³ Food and Drug Administration, "A Review of FDA's Approach to Medical Product Shortages," October 31, 2011. Available at: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM277755.pdf>

⁴ Alina Selyukh, "Study finds U.S. drug shortage problem concentrated," November 14, 2011. Available at: <http://www.reuters.com/article/2011/11/14/us-drugs-shortages-imshealth-idUSTRE7ADICJ20111114>

⁵ Alice Park, "Inside America's Drug Shortage," Time Magazine, March 19, 2012. Available at: <http://healthland.time.com/2012/03/19/where-have-all-our-drugs-gone/3/>.

⁶ Scott Hensley, "Drug Shortages Affect More Than Half A Million Cancer Patients," *National Public Radio*, November 15, 2011. Available at: <http://www.npr.org/blogs/health/2011/11/14/142311786/drug-shortages-affect-more-than-half-a-million-cancer-patients>

⁷ Ezekiel Emanuel, Shortchanging Cancer Patients, *New York Times*, August 6, 2011. Available at: http://www.nytimes.com/2011/08/07/opinion/sunday/ezekiel-emanuel-cancer-patients.html?_r=1.

⁸ Michelle Hudspeth, Testimony before House Committee on Oversight and Government Reform Subcommittee on Health Care, District of Columbia, Census, and the National Archives Hearing "Drug Shortage Crisis: Lives are in the Balance", November 30, 2011. Available at: <http://oversight.house.gov/hearing/drug-shortage-crisis-lives-are-in-the-balance/>.

⁹ American Society of Anesthesiologists, "Survey Reveals 90% of Anesthesiologists Experiencing Drug Shortages of Anesthetics," May 9, 2011. Available at: <http://www.asahq.org/For-the-Public-and-Media/Press-Room/ASA-News/Survey-Reveals-90%-of-Anesthesiologists-Experiencing-Drug-Shortages-of-Anesthetics.aspx>

such as rheumatologists, have been vocal that the drug shortages are causing them to change standard practices, often at much higher cost as name-brand drugs are substituted for generics.¹⁰ According to Dr. Ezekiel Emanuel, an oncologist, former advisor to President Obama, and professor of health policy at the University of Pennsylvania, “Most of these drugs have no substitutes, but, crazy as it seems, in some cases these shortages are forcing doctors to use brand-name drugs at more than 100 times the cost.”¹¹ Drug shortages can also disrupt clinical trials. Often, the drugs in shortage are used as controls to test the efficacy of new drugs.¹² If these generic drugs become unavailable during the course of the clinical trial, then the validity of the clinical trial – which can cost hundreds of millions if not billions of dollars – may be compromised.

II. Economics of Shortages

Normal Market Forces Prevent Shortages

Why can milk always be found at the grocery store and fuel is always available at the gas station, but scores of critical drugs are now unavailable to people who need them? In a well-functioning market, shortages are virtually nonexistent; and when shortages appear, they are resolved quickly. Basic economic theory shows that when a product becomes more scarce (either because supply has decreased, demand has increased, or some combination of the two), its price rises. The higher price provides an incentive for both consumers and suppliers. The higher price encourages consumers to cut back on consumption of the product and look for substitutes, and the higher price encourages suppliers to increase production since doing so will increase their profits. Some combination of increased production and tempered demand bring supply and demand back into balance.

Many of the drugs in shortage are critical for patients and lack adequate substitutes. Patient demand for critical drugs is not going to be significantly tempered by higher prices. This is particularly true since abundant third party payment of health care expenses means most patients do not actually experience the direct impact of rising prices. Therefore, the key question to answer with the current drug shortage crisis is what is limiting suppliers from producing enough of the critical drugs needed to satisfy patient demand.

Government Price Controls and Shortages

Economic theory suggests that the first place to look when product shortages persist is for the presence of government price controls.¹³ Price ceilings, maximum prices enforced by federal or state law, represent barriers to price flexibility. Price ceilings effectively prohibit prices from

¹⁰ Thomas Collins, “Rheumatologists Struggle with Drug Shortages,” *The Rheumatologist*, October 2011. Available at: http://www.the-rheumatologist.org/details/article/1361515/Rheumatologists_Struggle_with_Drug_Shortages.html

¹¹ Ezekial Emanuel, Shortchanging Cancer Patients, *New York Times*, August 6, 2011. Available at: http://www.nytimes.com/2011/08/07/opinion/sunday/ezekiel-emanuel-cancer-patients.html?_r=1.

¹² Heidi Ledford, “Drug shortage slows clinical trials: US researchers faced with cancer-drug shortfall struggle to keep trials on track,” *Nature*, October 3, 2011. Available at: <http://www.nature.com/news/2011/111003/full/news.2011.570.html>

¹³ For discussion, please see Hugh Rockoff, “Price Controls, *The Concise Encyclopedia of Economics*. Available at: <http://www.econlib.org/library/Enc/PriceControls.html>.

adjusting to the levels where consumer demand is tempered and suppliers are encouraged to increase production. As a result, supply and demand are not balance. Perhaps the most famous result from price ceilings in U.S. history is the presence of gas lines in the 1970s.¹⁴ An important economic truth is that while large government price ceilings hold down the money price, the total price, which includes the cost of waiting time and other inefficient rationing mechanisms, actually increases. Economists have shown that the large social welfare loss from this type of rationing far exceeds the benefit some consumers receive from artificially low prices.¹⁵ Clearly, rationing critical drugs through the use of waiting lists that can take months or years to clear is far more inefficient than somewhat higher drug prices.

Regulation and Shortages

Economic theory also shows that regulatory policy can play a powerful role in the overall amount of a production. For example, while regulation can provide certain benefits, regulation always produces corresponding costs. When industries confront a regulatory onslaught, the industries' costs rise. This means the industry must produce less of their product at a given price. If prices are constrained from rising, shortages can develop. In theory, regulations can also directly restrict supply through regulatory injunctions, which effectively shut down facilities.

III. Growing Market Concentration Laid the Groundwork for the Drug Shortage Crisis

Market-created Factors

Pharmaceutical companies typically do not sell products directly to hospitals and physician offices. Instead, manufacturers sell drugs to wholesalers and specialty distributors, who then sell the drugs to hospitals and physician offices. In addition, group purchasing organizations (GPOs) act as intermediaries by negotiating price and volume contracts with drug manufacturers on behalf of their members.¹⁶ GPOs, which emerged as a mechanism for providers to increase their buying power, assemble large networks of hospitals and clinics who agree to purchase drugs through a GPO. GPOs help health care providers realize savings by aggregating purchasing volume and using that leverage to negotiate price discounts with manufacturers.¹⁷ GPOs also use bundling to link price discounts to purchases of a specified group of products. About 98% of U.S. hospitals use GPO contracts to obtain price discounts, and hospitals use, on average, two to four GPOs.¹⁸

¹⁴ *Id.*

¹⁵ Fiona M. Scott Morton, "The Problems of Price Controls," *Regulation*, Spring 2001. Available at: <http://www.cato.org/pubs/regulation/regv24n1/morton.pdf>.

¹⁶ GAO, "Group Purchasing Organizations: Services Provided to Customers and Initiatives Regarding Their Business Practices," August 2010. Available at: <http://www.gao.gov/assets/310/308830.pdf>.

¹⁷ Health Industry Group Purchasing Association, *A Primer on Group Purchasing Organizations*, <http://www.higpa.org/> (accessed June 26, 2009).

¹⁸ *Id.*

In 2007, six GPOs accounted for over 90% of all hospital purchases made through GPO contracts across the country with the two largest GPOs having a nearly 60% market share.¹⁹ Manufacturers compete aggressively for GPO contracts because GPO networks represent a guaranteed source of demand. Since economies of scale in drug manufacturing translate into falling average cost as the amount of production increases, GPOs look for manufacturers that can produce drugs in high volume. Because of intense manufacturer competition to win GPO contracts, prices are driven down – the intended goal. As a consequence, however, companies that cannot produce a drug at large enough output levels to take advantage of the economies of scale – often because they lack the guaranteed source of demand that GPOs provide – will stop producing the drug or will neglect to enter the market.

Moreover, GPOs often provide suppliers with a preferred status or even an exclusive right to sell a particular product. If a manufacturer is not supplying any of the GPOs, but particularly the larger GPOs, with a particular product, much of the market is off limits. Since GPOs typically only offer preferred status to one manufacturer of a particular generic drug, and hospitals can be penalized for purchasing a significant amount of product from suppliers not affiliated with a GPO, the GPO structure reduces the number of manufacturers producing each generic drug.

Another problem is that GPO contracts contain clauses that limit price flexibility. According to a report by the Health and Human Services Office of the Secretary for Planning and Evaluation:

GPO contracts are generally in place for years and typically include price adjustment clauses. If a GPO is offered a lower price by a competing manufacturer, the original contracted manufacturer has a right of first refusal to match the new price. GPO contracts also typically include “failure to supply” clauses. These clauses generally require the manufacturer to reimburse the GPO for the price difference between the negotiated price and purchased price.²⁰

Since GPO contracts typically last three years, prices are prevented from making necessary adjustment to provide supplier with market information and with the incentive to switch production from drugs with less demand to drugs with greater demand. Once it is apparent that a drug is in shortage, GPOs go to great lengths to obtain the drug. However, the market-created GPO structure has created a climate that makes drug shortages more likely by reducing the number of manufacturers of each generic injectable medication. While it may not generally be a large problem to have only a few producers of each generic injectable medication, it becomes a problem when one, two, or even three of the producers of a given drug have manufacturing problems at the same time.

¹⁹ GAO, “Group Purchasing Organizations: Services Provided to Customers and Initiatives Regarding Their Business Practices,” August 2010. Available at: <http://www.gao.gov/assets/310/308830.pdf>.

²⁰ HHS Office of the Assistant Secretary for Planning and Evaluation, “Economic Analysis of the Causes of Drug Shortages,” October 2011, page 5. Available at: <http://aspe.hhs.gov/sp/reports/2011/drugshortages/ib.pdf>.

Legislative-created Factors

The Medicare Modernization Act (MMA), signed into law in 2003 by President Bush, has also reduced the number of suppliers of generic injectable medications. While the MMA is best known as adding a prescription drug benefit to the Medicare program, the MMA also changed the reimbursement rate for injectable drugs delivered in outpatient settings and capped the growth rate in Medicare's reimbursement paid to providers for administering these drugs. Before MMA, injectable drugs were reimbursed as a percentage of the drug's average wholesale price (AWP). AWP, however, was not a transparent way to understand the actual cost of producing these medicines. According to Dr. Ezekial Emanuel, an oncologist, former advisor to President Obama, and professor of health policy at the University of Pennsylvania, AWP was "a license to steal" against taxpayers because it was so inflated.²¹ MMA changed the law so that drugs delivered in the outpatient setting became reimbursed as a percentage of the average selling price (ASP)²² plus six percent. Moreover, the MMA limited increases in ASP to six percent semi-annually.

The ASP for name-brand drugs – drugs with patent protection – is relatively high since there is a single producer with considerable pricing power. Since companies producing name-brand drugs have a strong incentive to produce enough of the product to satisfy market demand, almost no name-brand drugs appear on the drug shortage list. When a drug comes off patent, the law allows one generic company to enter the market for a 180-day exclusivity period.²³ With only two manufacturers – the original manufacturer and the new entrant – the ASP is still relatively high, so producers have an incentive to continue producing these drugs. Moreover, because the company that gains the 180-day exclusivity period receives a temporary windfall profit, companies compete strongly to be the first generic producer.

After the 180-day exclusivity period, the market opens up for other entrants. Prices are driven down by market forces (competition) and expanded rebates and discounts given to the GPOs in an attempt to increase market share. According to Dr. Emanuel, "In the first two or three years after a cancer drug goes generic, its price can drop by as much as 90% as manufacturers compete for market share.... The low profit margins mean that manufacturers face a hard choice: lose money producing a lifesaving drug or switch limited production capacity to a more lucrative drug."²⁴ The figures on the next page demonstrate how quickly prices can decline when injectable drugs come off patent. Carboplatin, a chemotherapy drug primarily used to treat ovarian, lung, head, and neck cancers, came off patent in October 2004. Ondansetron, a drug used to prevent nausea and vomiting caused by chemotherapy, came off patent in December 2006. Irinotecan, a chemotherapy drug used to treat colon and rectal cancer, came off patent in February 2008. In the first year off patent, the prices of these three drugs declined 86%, 93%, and 86% respectively. Although falling prices are generally a positive development, problems arise if prices are not subsequently allowed to adjust to changing market conditions.

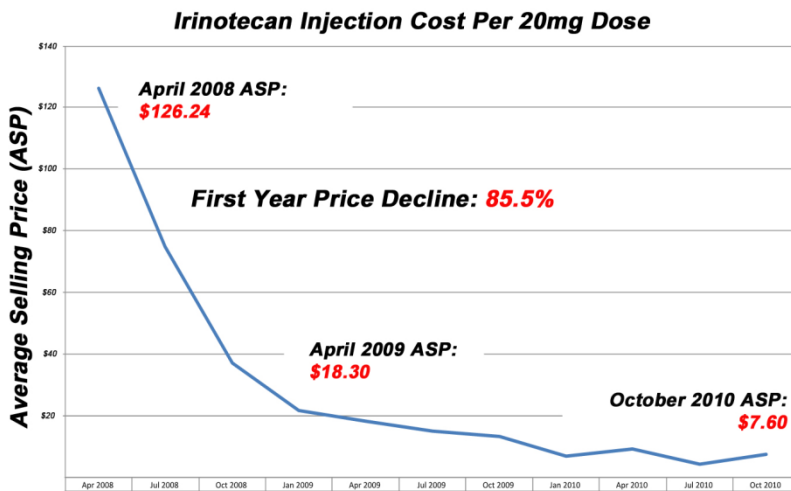
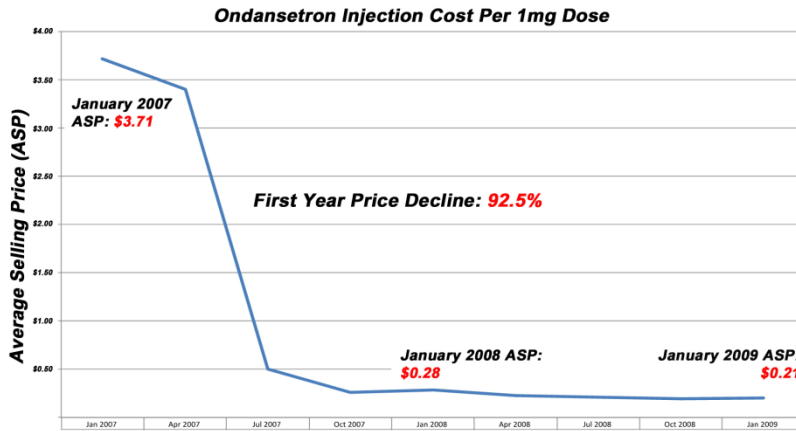
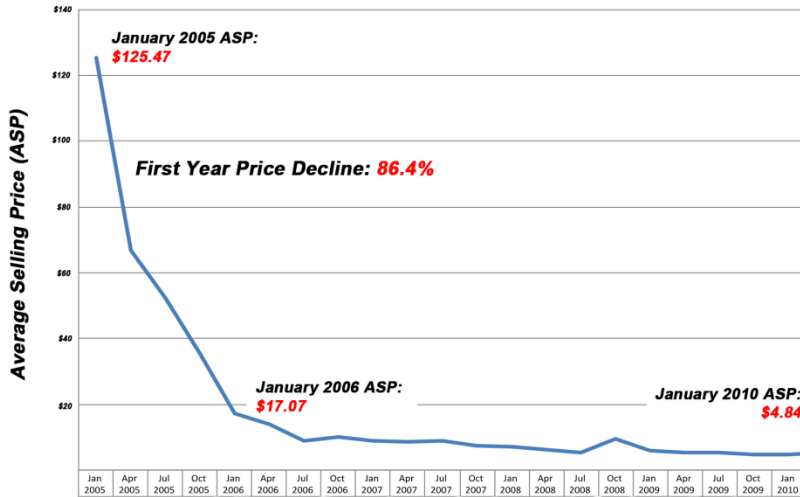
²¹ Staff phone call with Dr. Ezekial Emanuel, November 16, 2011.

²² ASP is what the manufacturer sells the drugs for minus the applicable discounts and rebates, given to grow market share.

²³ FDA, "Small Business Assistance: 180-Day Generic Drug Exclusivity." Available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069964.htm>.

²⁴ Ezekial Emanuel, Shortchanging Cancer Patients, *New York Times*, August 6, 2011. Available at: http://www.nytimes.com/2011/08/07/opinion/sunday/ezekiel-emanuel-cancer-patients.html?_r=1.

Figure 1: Price Changes for Generic Injectable Drugs Coming Off Patent
Carboplatin Injection Cost Per 50mg Dose



Source: CMS Quarterly ASP Files

Under normal market conditions, if a drug's price has been driven so low that manufacturers exit the market and switch to manufacturing other products, the drug's price would start to rise. The price increase would encourage other manufacturers to enter the market. However, since the MMA restricts price increases to six percent semi-annually and these increases are on top of very low prices, the increases do little to incentivize suppliers to expand production. According to pharmaceutical industry expert Walter Kalmans:

[I]f you were a generic injectable manufacturer with finite capacity, would you focus your capacity on manufacturing generics for products that have just lost patent protection, reaping high profits for the next few quarters, or would you manufacture lower priced generics, drugs whose patents expired long ago? . . . [B]ecause MMA limits price increases to 6% [semi-]annually, prices do not reach an equilibrium; even worse, because the profit potential of these drugs is so low, new entrants decide to stand on the sidelines or focus on more profitable products.²⁵

The Department of Health and Human Services Assistant Secretary for Planning and Evaluation (ASPE) has uncovered support for Mr. Kalmans' theory. According to an ASPE report:

Among the group of drugs that eventually experience a shortage, average prices decreased in every year leading up to a shortage. In contrast, the average prices of drugs that never experienced a shortage over this period did not change substantially either in the earlier or later period.²⁶

The MMA's changes only affected the reimbursement of drugs delivered in outpatient settings. Since oncology drugs tend to be administered in an outpatient setting, the Committee asked the five largest American manufacturers of generic injectable products whether they are producing a significant number of oncology drugs at a loss. According to one company, "[t]he rapid price declines and significant market shares controlled by a few customers often results in any number of manufacturers exiting the market because they have lost considerable market share and can no longer justify the manufacture of the product." While this answer highlights the problems from the MMA, it also points to the contributing role of the GPOs in increasing market concentration. **A second company responded that it is producing about three-quarters of its nearly two dozen oncology drugs at a loss, and the company believes that the MMA had the unintended effect of reducing prices to dangerously low levels:**

We note at the outset that the interplay of drug pricing and shortages is complicated, and the Medicare Modernization Act made that even more the case. We do believe that the government pricing methodologies (e.g., reimbursement based on ASP instituted by MMA, and so-called "penny pricing" under the 340B program) have reduced our margins and, in a number of cases, resulted in

²⁵ Walter Kalmans, Testimony before House Committee on Oversight and Government Reform Subcommittee on Health Care, District of Columbia, Census, and the National Archives Hearing "Drug Shortage Crisis: Lives are in the Balance", November 30, 2011. Available at: <http://oversight.house.gov/hearing/drug-shortage-crisis-lives-are-in-the-balance/>.

²⁶ For example, see HHS Office of the Assistant Secretary for Planning and Evaluation, "Economic Analysis of the Causes of Drug Shortages," October 2011, page 6. Available at: <http://aspe.hhs.gov/sp/reports/2011/drugshortages/ib.pdf>.

negative cash flows when compared to average non-Medicare pricing. . . . We believe that the MMA and other government pricing policies have had unintended consequences affecting our ability to make a reasonable profit margin, not only for our oncology products but also for certain other products.

Last month, the National Bureau for Economic Research published a working paper by Ali Yurukoglu on the connection between the MMA and the drug shortage problem.²⁷ His findings “provide evidence that the reactions of manufacturers to reducing health care expenditures likely reduced capacity and maintenance investments, and resulted in an increase in shortages.”²⁸ Yurukoglu found that drugs more affected by the policy change (those used predominantly by older patients) were more likely to be in shortage than drugs less affected by the policy change. The Committee’s findings, along with Yurukoglu’s research, provide substantial evidence that the MMA had a large and negative unintended consequence of increasing concentration in the generic injectable drug market and reducing company incentives to make upgrades to manufacturing lines producing those generic injectable drugs. However, most of the injectable drugs on the shortage list are primarily administered in hospitals and are not substantially impacted by the pricing changes made by the MMA. This suggests that there is a more significant cause of the widespread shortages than pricing problems.

IV. FDA’s Role in Causing the Drug Shortages

Like all government regulations, FDA’s regulation of the nation’s drug supply has benefits and costs. The main benefit of FDA regulation occurs when the agency prevents harmful drugs from reaching consumers. The main cost occurs when FDA action delays or prevents beneficial drugs from reaching consumers. Many economists have assessed the net benefit of FDA regulation by quantifying Type I errors (FDA allowing a harmful drug) and Type II errors (FDA disallowing beneficial drugs). Most studies have found that the harm from Type II errors far exceeds the harm from Type I errors, meaning FDA regulation too frequently prevents or delays life-saving and life-enhancing drugs and devices from reaching Americans in need.²⁹

Beginning in the late 1960s, drug approval time in the United States began to significantly exceed approval time in Europe. Researchers used the difference in drug approval speed to determine whether faster approval in Europe led to more unsafe drugs. Researchers compared product withdrawals in the United States with product withdrawals in Great Britain and Spain, each of which approved more drugs than the U.S. in the study period. They found no evidence that the United States had fewer recalls or that the drugs in the United States were

²⁷ Ali Yurukoglu, “Medicare Reimbursements and Shortages of Sterile Injectable Pharmaceuticals,” NBER Working Paper 17987, April 2012.

²⁸ *Id.*

²⁹ See e.g. Steven N. Wiggins. 1981. Product Quality Regulation and New Drug Introductions: Some New Evidence from the 1970s. *Review of Economics and Statistics* 63: 615-9; William M. Wardell and Louis Lasagna. 1975. [Regulation and Drug Development](#). Washington, D.C.: American Enterprise Institute for Public Policy Research; William M. Wardell. 1978. The Drug Lag Revisited: Comparisons by Therapeutic Area of Patterns of Drugs Marketed in the U.S. and Great Britain from 1972 through 1976. *Clinical Pharmacology and Therapeutics* 24: 499–524; Henry I. Miller. 2000. [To America's Health: A Proposal to Reform the Food and Drug Administration](#). Stanford, Calif.: Hoover Institution Press.

safer.³⁰ In another study, economists who compared the impact of FDA's extremely slow approval for a beta-blocker in the 1970s relative to approval time in Europe found that the FDA's delay was responsible for tens of thousands of premature deaths.³¹ Moreover, economist Samuel Peltzman found that many drugs are simply not developed because of stringent FDA regulations.³²

Many FDA experts believe the incentives of FDA officials to be risk-averse and focus on avoiding Type I errors relative to avoiding Type II errors to be a large part of the problem.³³ For example, when FDA allows a harmful drug, victims are identifiable and will likely cause shame and embarrassment for the agency. However, the victims who never gain access to drugs which are never developed are not identifiable.

Information obtained by the Committee shows that the FDA has not had a sufficient focus in ensuring access to and a continued supply of needed medicines over the last several years. Although manufacturers are reluctant to speak publicly about problems with their governing agency, the Committee found that the new political regime at FDA is largely to blame for the sudden spike of shortages that began in 2010. This conclusion is based on a months-long effort that included obtaining information from the five largest American suppliers (APP Pharmaceuticals, Bedford Laboratories, Hospira Pharmaceuticals, Sandoz Pharmaceuticals, and Teva Pharmaceuticals) of generic injectable medications and other experts. Although FDA's detection methods for finding minute impurities have improved, it appears FDA's enforcement and regulatory activities were unhinged from 2009 to 2011.

In June 2009, Margaret Hamburg became Commissioner of the FDA. Two months later, Commissioner Hamburg gave a speech at the Food and Drug Institute outlining her priorities and indicating that the FDA would significantly increase its enforcement activity and stringency:

When the FDA finds that a firm is significantly out of compliance, we expect a prompt response to our findings. Once the FDA provides inspection findings identifying a serious problem, the firm will generally have no more than fifteen working days in which to respond before the FDA moves ahead with a warning letter or enforcement action. This will help FDA issue warning letters on a timely basis and facilitate prompt corrective action. . . . [T]he FDA will take responsible steps to speed the issuance of warning letters. . . . **The FDA is fortunate to have received significant funding increases for the current and next fiscal year that will be devoted to additional inspection and compliance activities that**

³⁰ Olav M. Bakke, Michael Manocchia, Francisco de Abajo, Kenneth Kaitin, and Louis Lasagna. 1995. Drug safety discontinuations in the United Kingdom, the United States, and Spain from 1974 through 1993: A regulatory perspective. *Clinical Pharmacology and Therapeutics* 58: 108-17.

³¹ Sam Kazman. 1990. Deadly Overcaution. *Journal of Regulation and Social Costs* 1, no. 1: 35-54; Dale H. Gieringer. 1985. [The Safety and Efficacy of New Drug Approval](#). *Cato Journal* 5, no. 1: 177-201.

³² Sam Peltzman. 1973. [An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments](#). *Journal of Political Economy* 81, no. 5: 1049-91. Reprinted in *Chicago Studies in Political Economy*, edited by George J. Stigler, 303-48. Chicago, University of Chicago Press, 1988.

³³ Alex Tabarrok and Daniel Klein, "Why the FDA Has an Incentive to Delay the Introduction of New Drugs," [FDAREview.org](#). Available at: <http://www.fdareview.org/incentives.shtml>; Henry I. Miller. 2000. [To America's Health: A Proposal to Reform the Food and Drug Administration](#). Stanford, Calif.: Hoover Institution Press.

will support the elements of an effective enforcement strategy that I have outlined.³⁴ [emphasis added]

As a result of the FDA's intensified inspection and compliance efforts to "facilitate prompt corrective action," four of America's five largest manufacturers of generic injectable products have taken unprecedented and *simultaneous* remediation efforts. Remediation efforts are company efforts to resolve compliance issues raised by the FDA in a warning letter or required by a consent decree of permanent injunction.³⁵

Since December 2009, each of the manufacturers who have shut down production lines in the past year received FDA warning letters for their facilities that manufacture generic injectable medications. The warning letters each contain this explicit threat of enforcement action:

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction.³⁶

The graph on the next page shows that the number of FDA warning letters has increased dramatically over the past two years. In the first year that Margaret Hamburg was FDA Commissioner, the number of warning letters increased 42% – from 474 letters to 673 letters. In Margaret Hamburg's second year as FDA Commissioner, the number of warning letters increased a staggering 156% – up to 1,720 letters. While these figures include all FDA warning letters across all areas, they clearly show a dramatic change in FDA's regulatory approach.

The simultaneous remediation effort undertaken by America's manufacturers of generic injectable medications is problematic since virtually all injectable drugs used in the United States are manufactured in the United States.³⁷ Prior to their remediation efforts, Hospira, Teva, Bedford, and Sandoz were producing nearly one billion units of generic injectable products per year. **Facilities at these companies are currently operating at about 700 million units per year, a 30% decrease in manufacturing capacity at America's primary production facilities for generic injectable drugs. This decrease is a massive reduction in the industries' capacity to supply the nation with injectable medications.** Pharmaceutical companies, despite running available production lines around the clock, are now forced to decide which drugs to

³⁴ Remarks by FDA Commissioner Margaret A. Hamburg on "Effective Enforcement and Benefits to Public Health" at Food and Drug Law Institute, August 6, 2009. Available at: <http://www.fda.gov/NewsEvents/Speeches/ucm175983.htm>

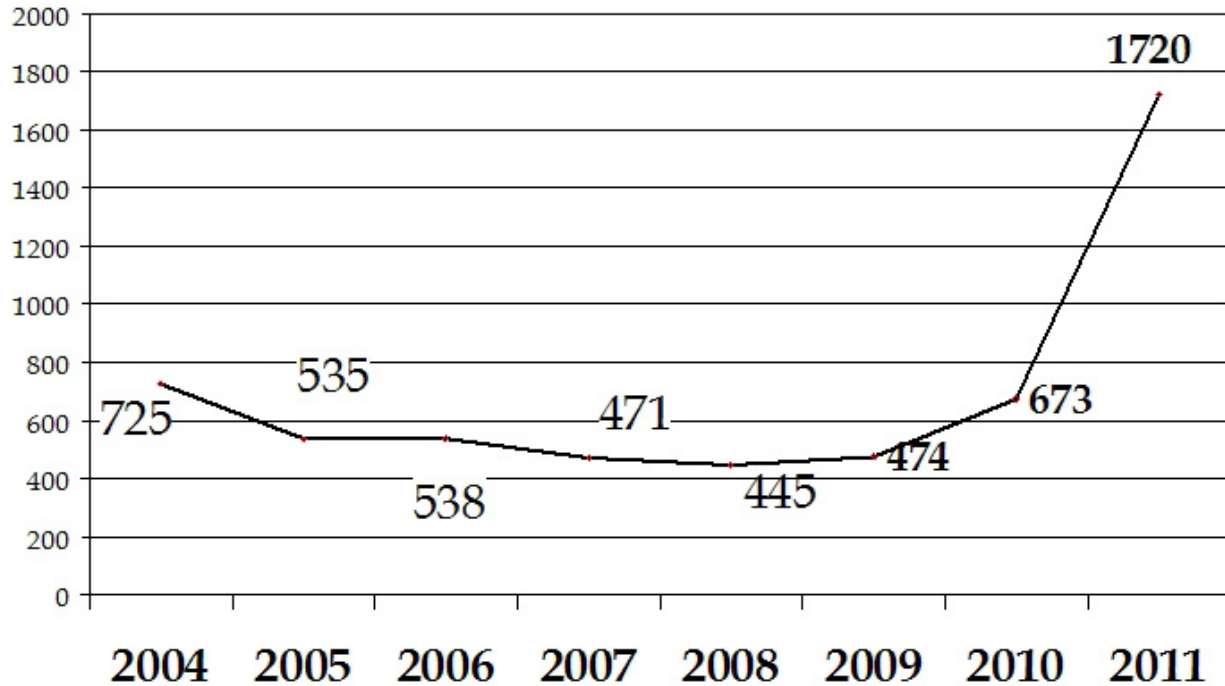
³⁵ The FDA defines as warning letter as: "[A] correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations. Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected. A Warning Letter is one of the Agency's principal means of achieving prompt voluntary compliance with the Act." Food and Drug Administration, "Procedures for Clearing FDA Warning Letters and Untitled Letters," December 2010. Available at: <http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM176965.pdf>.

³⁶ FDA Inspections, Compliance, Enforcement, and Criminal Investigations letter to Teva Parenterals Medicines, Inc., December 11, 2009. Available at: <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm209222.htm>.

³⁷ HHS Office of the Assistant Secretary for Planning and Evaluation, "Economic Analysis of the Causes of Drug Shortages," October 2011, page 6. Available at: <http://aspe.hhs.gov/sp/reports/2011/drugshortages/ib.pdf>.

continue producing and which to stop producing, and whether to cease production temporarily or permanently. Since generic injectable producers earn low marginal profits for older generic injectable medications, companies have an incentive to cease their production when their capacity is restricted.

Figure 2: FDA Warning Letters, Fiscal Years 2004 – 2011



Source: FDA Fiscal Year 2011 Enforcement Statistics³⁸

According to testimony by Dr. Scott Gottlieb, former deputy commissioner of the FDA and senior policy advisor to the Centers for Medicare and Medicaid Services, the FDA has largely contributed to the drug shortage crisis with inflexible and outdated policies:

With its vigilance heightened, the FDA has required manufacturers to undergo major plant renovations, suspend facilities or stop shipping goods from suspect production lines. The FDA and the manufacturers often don't understand the drug-production processes well enough to detect the root cause of problems. Instead of calling for targeted fixes of troubled plants, the agency has often required manufacturers to undertake costly, general upgrades to facilities. As a result, in 2010, product quality issues – and the subsequent regulatory actions

³⁸ FDA Inspections, Compliance, Enforcement, and Criminal Investigations, "FY 2011 Enforcement Activity." Available at: <http://www.fda.gov/ICECI/EnforcementActions/ucm247813.htm>.

taken by FDA to address these problems – were involved in 42% of the drug shortages.³⁹

According to the information obtained by the Committee, the number of drugs in shortage that are produced in at least one facility undergoing remediation efforts has grown. Of the 219 drugs listed on the ASHSP shortage list as of February 21, 2012, at least 128 (58% of all drugs on the shortage list) were being produced by at least one facility undergoing FDA remediation.⁴⁰ The Committee could not find any evidence that any products produced – many of which have been produced for decades – at the facilities undergoing remediation had harmed anyone beyond typical side effects associated with any type of medication.⁴¹ According to one company:

[T]here [have] not been any specific concerns denoted with regard to the safety, purity, or quality of [our] products at this facility [undergoing FDA remediation.] [We have] voluntarily taken these actions to update product validations to **current expectations**. [emphasis added]

This general comment echoes the sentiments of most of the other companies which are remediating facilities to satisfy FDA requirements. While this company stated its actions were “voluntary”, the actions were taken in response to an FDA warning letter which indicated compliance was necessary to avoid FDA enforcement. According to David Gaugh, senior vice president for regulatory sciences at the Generic Pharmaceutical Association, “[T]he FDA has been much more aggressive in their inspection formats over the past two to four years.”⁴²

One obvious question that FDA should answer is why nearly all of America’s major producers of generic injectable medications were essentially required to remediate facilities at the same time. It was this simultaneous remediation that reduced available capacity at these facilities by 30% relative to capacity in 2009. For facilities with genuine manufacturing problems, it would have been more prudent to focus on directing facilities to make targeted improvements under close supervision of the FDA. Such a targeted approach would have significantly diminished the public health crisis the country is facing from the abundant number of drug shortages.

According to sources with inside information about FDA’s operations, there is a disconnect between the FDA field force, the inspectors who work out of the agency’s district offices, and scientists and other career individuals at FDA headquarters who work on review and compliance functions. The job of the field force is to perform site inspections and issue citations.

³⁹ Scott Gottlieb, Testimony before House Committee on Oversight and Government Reform Subcommittee on Health Care, District of Columbia, Census, and the National Archives Hearing “Drug Shortage Crisis: Lives are in the Balance”, November 30, 2011. Available at: <http://oversight.house.gov/hearing/drug-shortage-crisis-lives-are-in-the-balance/>.

⁴⁰ Several smaller generic drug manufacturers have also been subject to FDA warnings and have undergone remediation efforts. Therefore, 128 is a lower bound because only FDA’s actions against the five largest manufacturers of generic injectable drugs were tabulated.

⁴¹ There were concerns about glass particulates in a few vials of drug produced by Bedford at its Ben Venue facility and a few vials of a drug produced by Sandoz at its Boucherville facility. In both cases, the vials were part of a production lot that was voluntarily recalled.

⁴² Alice Park, “Inside America’s Drug Shortage,” Time Magazine, March 19, 2012. Available at: <http://healthland.time.com/2012/03/19/where-have-all-our-drugs-gone/3/>.

According to the Committee's sources, FDA's field force does not believe that it is within the scope of their authority to worry about the implications of their actions, even if it means a manufacturer closing a facility or removing manufacturing lines from production. The 250% increase in warning letters between fiscal year 2009 and fiscal year 2011 and the serious shortage of injectable drugs provides evidence that the field force has become much more aggressive.

Although field staff zealotness increased starting in mid-2009, there are indications that by mid-2011 the FDA was at least aware there was a relationship between FDA enforcement activities and the drug shortage problem. For example, the FDA's warning letters to Teva on December 11, 2009 and to Hospira on April 12, 2010 did not contain any reference to the drug shortage crisis, but its warning letters to Sandoz on November 18, 2011 and to APP on February 22, 2012 did contain the following directive:

If as a result of receiving this Warning Letter or in general, you are considering making a decision that will result in a decreased number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov in order to ensure that your action(s) does not adversely affect the public health.⁴³

FDA regulatory actions need to be put in proper context. Companies have strong incentives to maintain quality, even absent FDA regulations. If drug manufacturers produce drugs that are unsafe or ineffective, they risk losing business or going out of business from market competition. Moreover, the threat of tort lawsuits incentivizes manufacturers to produce safe and effective drugs. While some amount of FDA oversight is desirable, if regulators fail to account for the incentives that already exist for market participants to produce safe and effective drugs, they are prone to over-regulate. FDA's regulators are always going to be able to find flaws at any facility if they are determined to find flaws; the key is whether the flaws pose a real danger to patient health. In a common sense regulatory approach, there would not be a simultaneous remediation effort at four of the five largest American producers of generic injectable products creating significant shortages. Tragically, the cost of shutting down production lines seems to have vastly exceeded the corresponding benefits.

V. Conclusion

Many of the reasons that have been offered to explain the drug shortage crisis, from increased demand for drugs to raw material disruptions, fail to provide adequate answers to two key questions – why the number of drugs in shortage began spiking in 2010 and why the vast majority of the drugs in shortage are generic injectable medications. Several experts, including Dr. Scott Gottlieb and Dr. Ezekial Emmanuel, as well as a recent academic paper by Ali Yurukoglu, have attributed part of the problem to the Medicare Modernization Act (MMA). The MMA decreased reimbursements that Medicare pays for administering injectable medications to levels that are often below the cost that it takes for manufacturers to produce the drugs.

⁴³ FDA Inspections, Compliance, Enforcement, and Criminal Investigations letter to APP Pharmaceuticals, LLC, February 22, 2012. Available at: <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm209222.htm>.

Manufacturers are reluctant to raise prices for these drugs above what Medicare reimburses providers who administer them. According to information obtained by the Committee, manufacturers are currently producing many oncology drugs at a loss.

Regardless of industry, when a supplier is losing money on a particular product they have an incentive to shift production to a product that earns a profit. Therefore, common sense suggests that the MMA would lead to fewer suppliers producing oncology drugs and the evidence indicates this is exactly what has happened. Group purchasing organizations (GPOs) have also contributed to both inflexible prices in the market for generic injectable drugs and growing market concentration. Inflexible prices lead to shortages by effectively distorting market signals that incentivize suppliers to produce more of certain drugs and less of others. Moreover, generic producers who fail to ascertain GPO contracts for particular drugs have little incentive to manufacture those products. While this may not normally be a significant problem, it becomes a problem if there are only one or two producers and manufacturing difficulties arise.

The main effect of the MMA and GPO contracting has been to increase concentration in the generic injectable industry as fewer companies are producing individual generic medications. Despite FDA's awareness of growing industry concentration, FDA began a sweeping policy in mid-2009 that would force America's largest producers of generic injectable medications to upgrade facilities. It appears that FDA's political appointees unleashed its field force to issue a flood of broad warning letters to manufacturers. It is not a coincidence that nearly every major American manufacturer producing generic injectable medications has undertaken large scale facility remediation during the past two years. Rather, under the threat of FDA enforcement activity, manufacturers have decided to make large scale facility upgrades *simultaneously* with a resulting loss of 30% of industry manufacturing capacity. Last year, a report from the Assistant Secretary for Planning and Evaluation at HHS acknowledged the risk from shutting down manufacturing lines:

This temporary closure of a large manufacturing facility can also lead to other facilities being unable to meet the increased demand for the drug due to the lack of excess capacity and the pressure of ramping up supply for multiple drugs in other facilities.⁴⁴

While many of the facilities were older and the upgrade to certain facilities was desirable, the simultaneous, large-scale shutdown of manufacturing lines at most major domestic producers of generic injectable drugs has plunged America into a public health crisis.

FDA has responded to the drug shortage crisis by increasing resources in its Office of Drug Shortage. Essentially, FDA is now attempting to address a problem that is largely of FDA's own making. Although FDA claims to be preventing or resolving scores of drug shortages, the number of drugs in shortage continues to rise. FDA's Office of Drug Shortage is engaging in an attempt to obtain information about drugs that are at risk of shortage and then making requests of suppliers who are able to increase production of a drug at risk of shortage. Unfortunately, this level of centralized planning is necessary when prices no longer contain

⁴⁴ HHS Office of the Assistant Secretary for Planning and Evaluation, "Economic Analysis of the Causes of Drug Shortages," October 2011, page 13. Available at: <http://aspe.hhs.gov/sp/reports/2011/drugshortages/ib.pdf>.

useful information about the relative scarcity of drugs. Even more unfortunate, because of the huge loss of manufacturing capacity, FDA's actions will likely fail to reduce the number of drugs in shortage. Rather, FDA's actions are only likely to shift which drugs are in shortage at any given time.

According to America's companies manufacturing generic injectable medications, it will be another two or three years before manufacturing capacity returns to where it was before FDA's widespread remediation efforts. Once these facilities are completely remediated, the drug shortage crisis will likely end. However, for a five-year period (2010 – 2014), patients and doctors will have suffered with the results, such as premature death, inferior treatment regimes, and higher health care costs, of the widespread shortages. It is important to acknowledge that the overall damage inflicted by the FDA's lack of regulatory balance extends beyond the drug shortage crisis. Rather, the drug shortages are only the most visible result, thus far, of the FDA's stepped up enforcement activities.

VI. Recommendations

- A common sense approach to regulations must be restored at the FDA. Agency protocols should be revised so that the agency is required to consider the implications of its actions on the nation's supply of critical drugs.
- The drug shortage crisis has shed greater transparency on the dysfunctional price system that governs generic injectable medications. To improve the price mechanism, Congress should reform the way that Medicare pays for drugs so the program's reimbursements better reflect actual supply and demand conditions in the market.
- Proposals to allow drug companies to share information about each other's manufacturing capability and product availability may have merit because of the extraordinary circumstances of the present drug shortage crisis. However, this type of information sharing potentially places consumers at risk as a result of collusion by the large manufacturers.