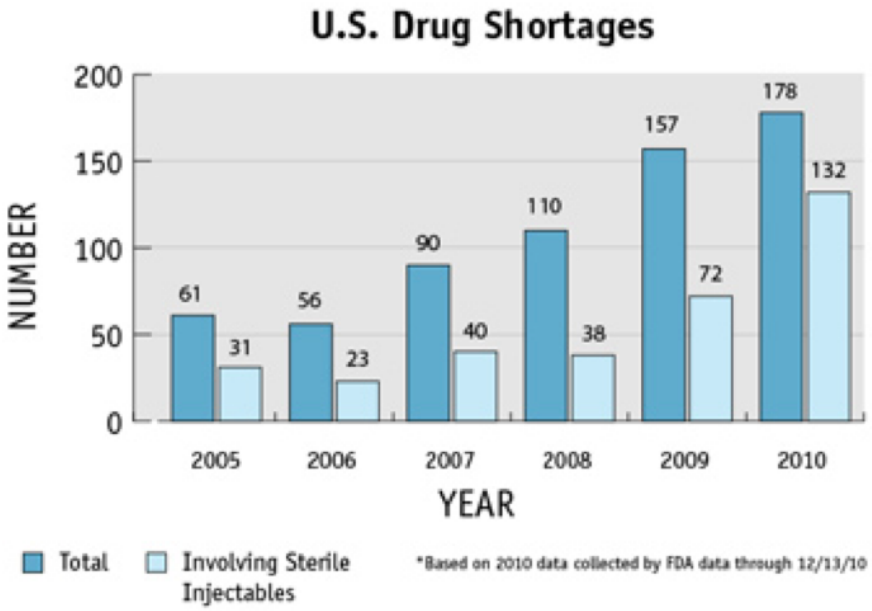
I. Background on the Problem

Currently, there are over 150 drugs listed on the FDA drug shortage list and the problem is getting worse. Essentially all of these drugs are generic compounds without proprietary protection.

Figure 1: Drug Shortage Increasing: Injectables the Biggest Problem



Source: FDA; *FDA Works to Lessen Impact of Drug Shortage*
http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm258152.htm

As noted from this data, the increase in the number of drugs in short supply has been driven largely by an increase in shortages of sterile injectable drugs.

Oncology has borne the brunt of the shortage because critical oncology drugs are mostly sterile injectables but also there are few or no known substitute drugs available and the drugs in short supply are life-saving or life-prolonging. Critical oncology drugs in short supply include:

Cytarabine	5-FU
Daunorubicin	Cisplatin
Doxorubicin	Paclitaxel
Leucovorin	

These factors have led to greater media exposure of the problem including opinions and articles in the New York Times.

II. Current Industry Environment

The pharmaceutical supply chain involves many different parties who contract with one another in order to maximize their own interest. These parties include the manufacturer, distributor, and group purchasing organization, pharmacy, physician, patient and third party payer.

Pharmaceutical products face 2 major barriers to product introduction: intellectual property and regulatory control for labeling and quality. Proprietary compounds that pass the regulatory hurdle for market entry command a very high price and margin due to minimal direct product competition and little or no pricing competition even if there are other proprietary alternatives.

Once the intellectual property for a drug has expired, the barriers to entry by another manufacturer drop dramatically. This includes a substantially reduced regulatory burden for entry. The main emphasis of regulatory control for small molecule injectable products shifts completely to chemical, manufacturing and quality control issues with no clinical burden of proof. The regulatory and intellectual property barriers to generic drug entry into the market were reduced dramatically after passage of the Hatch-Waxman act in 1983 leading to the expansion of the generic drug industry.

This legislation was designed to unify patent terms by changing the start and term of patents from 17 years after the grant date to 20 years from the filing date. In addition, the legislation streamlined the generic drug approval process. The effect of the legislation is summarized in Table 1.

Table 1: The Effect of the Hatch-Waxman Legislation on Generic Drugs

Parameter	Before H-W	After H-W
Patent Term (years)	17 from grant	20 from filing
Avg. Period of Market Exclusivity	9 years	11.5 years
Period from patent expiry to generic entry	3-4 years	1-3 months
Avg. Generic market share	12.7%	57.6%

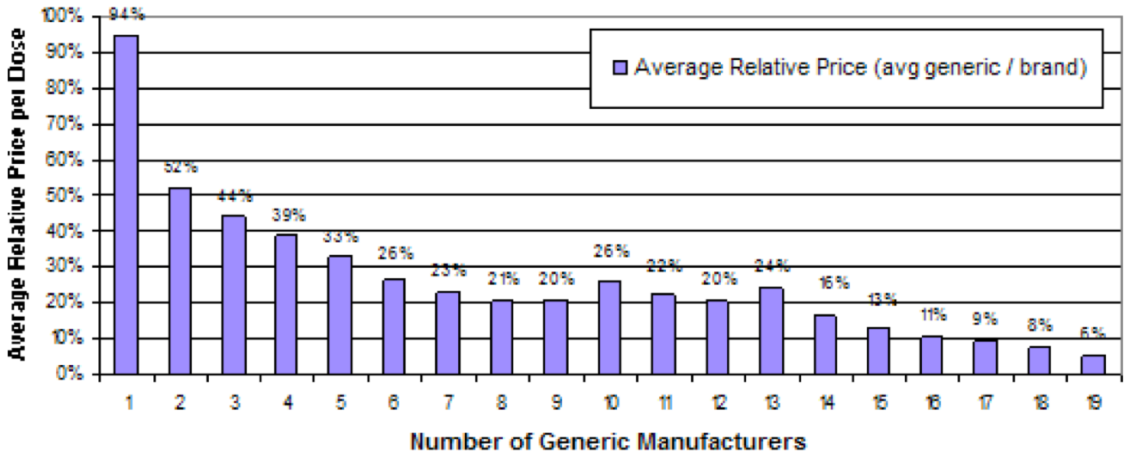
Source: Congressional Budget Office: HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY. 1998, http://www.cbo.gov/doc.cfm?index=655&type=0&sequence=5

As can be seen, the legislative changes resulted in a dramatic reduction between the time of patent expiration and generic competition entry into the market. In addition, the average market share for generic drugs rose from 12.7% before the legislation to

57.6% after the legislation. These data reflect the enormous growth of the generics industry in the US.

As more generic manufacturers entered the market, the cost of drugs fell dramatically. Figure 2 shows the effect of introducing generic competition on price.

Figure 2: Generic Competition and Drug Prices



Source: FDA; *FDA analysis of retail sales data from IMS, IMS National Sales Perspective(TM), 1999-2004 extracted February 2005.*

The first 4-5 entrants into the market consume the vast majority of the profit margin. While there may be further price reduction as additional manufacturers enter the market, the return to those manufacturers is substantially less than the first entrants.

Inevitably, these price reductions reduce substantially the profit margin for each drug. Therefore, the generic drug manufacturers seek to protect their profit margin by reducing manufacturing costs as much as possible. Among the variables that impact manufacturing cost include:

1. Physical manufacturing plant capacity
2. Manufacturing batch size; typically tied to sales volume
3. Cost of materials
4. Complexity of the process
5. Stability of inventory
6. Extent of quality control required
7. Indirect expenses

The regulatory burden is substantial to maintain your manufacturing approval. A framework of Guidance Documents from regulatory authorities referred to as Good Manufacturing Practices or GMP tightly controls the manufacturing process. A key exacerbating event in the genesis of the shortage has been a failure by some generic manufacturers to maintain GMP conditions. These conditions must be met for FDA to

allow continued manufacturing of any pharmaceutical product. GMP manufacturing conditions follow a few basic principles.

1. Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.
2. Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary.
3. Instructions and procedures are written in clear and unambiguous language.
4. Operators are trained to carry out and document procedures.
5. Records are made, manually or by instruments, during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected. Deviations are investigated and documented.
6. Records of manufacture (including distribution) that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.
7. The distribution of the drugs minimizes any risk to their quality
8. A system is available for recalling any batch of drug from sale or supply.
9. Complaints about marketed drugs are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective drugs and to prevent recurrence.

Appendix B outlines the manufacturing process in detail.

A new manufacturer entering the market must generate data and submit to FDA an Abbreviated New Drug Application (ANDA). If successful, the ANDA process grants approval for the manufacturer to sell and distribute a specified drug. The key components of the application are chemistry, manufacturing equipment and process and quality controls. Chemistry includes both process chemistry and analytical chemistry. Manufacturing plant and equipment specifications and design must be included. All aspects of quality controls including in-process checks, release testing, batch approval and investigations are included. Data must be generated on the robustness of the manufacturing process, analytical chemistry, and stability. The data is compiled and submitted in an application after which FDA is allowed 18 months to review and take action. Should FDA raise significant questions, this time may be substantially delayed.

Once established the generic drug price is established, it remains relatively unchanged due to both market pressure and regulatory price controls. Manufacturers must tightly manage their cost parameters to maintain a profitable margin. At low established margins with multiple manufacturers, there is little or no incentive for new manufacturers to invest the time and money to overcome regulatory barriers to become another competitor. Over time, existing manufacturers compete for volume based on available leverage including their ability to bundle multiple products to sell at a price attractive to both the manufacturer and the distributer. As the market for a given drug evolves, some manufacturers suffer failed profitability due to low sales volume, poor cost control and rapid price erosion leading some manufacturers to stop supplying the market. Over time, business gravitates to fewer manufacturers who control the volume.

This concept of market maturity is very well illustrated by looking at the active versus

inactive ANDA holders for an older versus a newer shortage drug. Table 2 shows this data for 5-FU. There are a total of 15 active and inactive ANDAs while only 5 are active and only 3 are supplying the market (FDA Orange Book and Appendix B).

Table 2: Active and Discontinued ANDAs for 5-FU

ANDA	Company
Active	AP Pharma
	Bioniche Pharma
	Ebewe Pharma
	Sandoz
	Teva
Discontinued	ABIC
	Abraxis
	APP Pharma
	Bedford
	Marchar
	Pharm Upjohn
	Smith Nephew
	Teva
	Valeant
	Watson

Source: FDA; *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If a supply shortage occurs, the typical resultant supply and price increases are suppressed by limited capacity and regulatory price controls. Once a given manufacturer's price is established, they cannot raise the price more than 6% above the trailing 6-month sales price. Therefore, if there are significant supply/demand imbalances prices do not serve as a strong counteracting force to rapidly change supply or demand such as they due in unregulated markets.

Disruptions in the supply from the shutdown of the Teva Irvine plant and problems at the Bedford plant have lead to shortages for 5-FU and many other oncology drugs. Teva and Bedford are listed on the FDA shortage page for essentially every oncology drug in short supply. These manufacturing quality issues account for much of the shortage.

Large manufacturing companies with established sales channels and high volume have a distinct advantage in the generic drug market. Any new entrants into the market must have a significant advantage such as a lower cost structure, superior distribution or broader sales capability. The major generic drug companies are listed in Table 3.

Table 3: Top 10 Generic Drug Manufacturers

Rank	Company	Location	Annual Rev. ($B)	Market Share (%)
1	Teva	Israel	6.956	21.8
2	Mylan	Pitt. PA	3.620	11.3
3	Sandoz	Germany	2.494	7.8
4	Watson	Corona, CA	2.0	6.3
5	Greenstone/Pfizer	Peapack, NJ	1.721	5.4
6	Par Pharma	Woodruff, NJ	1.319	4.1
7	Hospira	Lake Forest, IL	1.061	3.3
8	Apotex	Canada	0,879	2.8
9	Mallinckrodt	Hazelwood, MO	0.860	2.7
10	Dr. Reddy's	India	0.834	2.6

Source: Fierce Biotech August 10,2010: *Top 10 Generic Drug Companies 2010* by Liz Jones Hollis.
http://www.fiercepharma.com/story/top-10-generic-drug-companies-2010/2010-08-10

From this list, the top generic drug manufacturers of generic oncology drugs appear to be Teva and Hospira although there are low volume manufacturers that appear frequently on the drug shortage list for oncology drugs and those companies include Bedford Labs and AP Pharma (Appendix C).

Pharmaceutical wholesale distributors provide logistics and warehousing services to pharmaceutical manufacturers. They receive product from the manufacturer at a contracted price and assure delivery to the end user of injectables via their specialty distribution arm, typically to a community oncology practice. In the event that a manufacturer cannot supply a contracted product often times a differential clause is triggered causing the manufacture to pay the price differential for all products purchased from a secondary source.

Table 4: Top 5 Oncology Drug Distributers

Distributor
McKesson
AmerisourceBergen
Cardinal Health
Oncology Supply
OTN

Source: *Healthcare Market Overview: Oncology Purchasing and Distribution Groups*. Knowledge Source, June 2011.

Physicians and physician groups have suffered substantially due to the shortage. Of primary importance is the frustration of not being able to administer known life-saving therapies to their patients. Because the end users of pharmaceuticals are not naturally aggregated in large pools relative to the distributors, group purchasing organizations (GPOs) have arisen in order to leverage end user combined purchasing power to

negotiate better economic terms from distributors or manufacturers. In oncology, the largest GPO is US Oncology (McKesson) and ION (Amerisource Bergen); these GPO's were purchased by the larger wholesalers indicating a continued trend to vertically integrate distribution services with other value added approaches aimed at oncology practices consolidation. The major oncology suppliers are listed in Table 5.

Table 5: Oncology Group Purchasing Organizations

GPO	Location
Amerisource Bergen (ION)	Frisco, TX
Bellwether Oncology Alliance	Nashville, TN
CMED Oncology	Waterford, CT
Community Hem/Onc Consortium	Phil, PA
SelectPlus/USO (McKesson)	SF, CA
New Jersey Society of Onc Managers	NJ
Oncology Ass. Physician Network Services	Chesterland, OH

Source: *Healthcare Market Overview: Oncology Purchasing and Distribution Groups*. Knowledge Source, June 2011.

However, end users have generally not aggregated themselves cohesively into a large enough GPO to extract substantial demands from the manufacturers and suppliers. Rather, the suppliers have purchased the GPO's somewhat abrogating the leverage of the end user.