



**June 21, 2012**

**Fixing Drug Shortages**

***By Peter J. Pitts***

In August of 2011, Zeke Emanuel wrote an op-ed in the Sunday New York Times titled, “Shortchanging Cancer Patients” – and drug shortages became a hot national issue almost overnight. Unfortunately, it’s not a new problem.

Today, with political and media attention – and PDUFA -- we have the real opportunity not to fix the blame, but to fix the problem. Let’s start with the FDA.

The Institute for Safe Medication Practices surveyed 1,800 healthcare practitioners, and found more than half of respondents frequently or always encounter difficulties associated with drug shortages.

The top three problems fall squarely within the zone of appropriate FDA attention and action. They include:

- \* Little or no information available about the duration of a drug shortage (85%)
- \* Lack of advanced warning from manufacturers or FDA to alert practitioners to an impending drug shortage and suggested alternatives (84%)
- \* Little or no information about the cause of the drug shortage (83%)

Survey respondents felt “unsupported” by the FDA. That needs to change and it is changing with a more robust FDA program.

The FDA’s Drug Shortage Program (DSP) resides within the FDA’s Center for Drug Evaluation and Research. The DSP works with pharmaceutical manufacturers, review divisions, compliance, and other components of the agency to manage product shortages

through communication, facilitation, and negotiation.

When the shortages are for generic products, the FDA works with other firms making the drug to help them ramp up production if they are willing to do so. Often they need new production lines approved or new raw material sources to help increase supplies. FDA can and does expedite review of these facilities to help resolve shortages of medically necessary drugs.

But the FDA can't require firms to increase or commence production.

The agency tries to do the best it can with limited authority, spare resources, and shared staff. In addition to direct communication with industry, the DSP also gets reports from healthcare professionals, patients and professional organizations.

It's a good start – but it's just a start -- and we must be cautious of hyperbole.

According to FDA Commissioner Peggy Hamburg, since President Obama gave the agency new authorities, shortages have fallen (year-to-year) by more than half. There have been 42 new shortages in 2012 compared to 90 at the same time last year.

That's good news, but is this decline really due to the FDA's ability to demand earlier information about potential shortages from manufacturers?

"I am both amazed and delighted to see the progress that's been made, said Commissioner Hamburg. Key word: "Amazed."

While the FDA's new authorities are both timely and important, there are many pieces to the drug shortages problem – not the least of which is that (when it comes to hospital injectables) 30% of manufacturing capacity is off-line due to FDA inspection issues. That's a lot of capacity. In fact, according to the agency, 43% of reported potential shortages were due to manufacturing problems.

Safety is non-negotiable and alleviating a shortage by shorting GMPs is a bad and dangerous pathway. Expediency causes as many problems as it solves.

That being said, regulatory discretion must be part of the solution. With 30% of production capacity off-line because of FDA issues, the agency must work with manufacturers to find creative, science-based solutions. If you create a "science- and risk-based action plan," industry can often address quality issues without disrupting supplies of essential drugs.

The FDA might allow some temporary fixes that fall in line with that thinking. According to the FDA's Jouhayna Saliba (senior regulatory program manager at the FDA's Drug Shortage Program). If a company discovers impurities that could be filtered out, the agency might allow the product to be shipped along with filters and explanations of how they are to be used in order to avoid a shortage, she said.

But who inspects the inspectors? Per that 30% of manufacturing capacity off-line due to FDA issues, perhaps the FDA should undertake an agency audit to see why there's been such a jump in GMP issues. It's hard to believe that year-over-year, production quality control has suffered such a significant lapse. Is there something wrong in the way FDA inspectors (many of them still wet behind the ears and eager to please) are doing their jobs? It's a question worth asking – and answering.

A 30% hole in manufacturing is more than a hint that something's amiss both with manufacturers – and at White Oak.

While earlier and more robust communications between drug manufacturers (largely generic manufacturers of hospital injectables) and the FDA is important – lack of such interaction isn't the major cause of the problem.

Plainly speaking, artificially low prices are the major cause drug shortages.

A US government analysis of average sales prices shows that oncology sterile injectables that experienced shortages since 2008 decreased in price from \$56.17 per unit in Q1 2006 to \$37.88 per unit in Q1 2011.

Oncology sterile injectable drugs that have *not* experienced shortages have had relatively stable prices over this same period.

Most of the drug shortages that occur in the U.S. arise in the generics market, where profitability is fairly low. For many of these drugs the market can only sustain a handful of manufacturers -- sometimes just one or two. So, when supply disruptions occur -- caused by manufacturing violations, production delays, shipping problems or ingredient issues -- there aren't a lot (or in many cases *any*) additional producers in the market to pick up the slack.

Exacerbating the problem, as generic manufacturers consolidate, there are fewer and fewer plants left making certain drugs.

A highly related and relatively unreported problem is the role of Group Purchasing Organizations (GPOs). GPOs control the purchasing of more than \$200 billion in drugs, devices, and healthcare supplies annually for some 5,000 private, acute care hospitals nationwide.

GPOs have created a concentrated market that excludes other existing and would-be suppliers. And with no other suppliers able or available to fill the gap, increases in demand for generic drugs have resulted in shortages and rising prices.

It is no coincidence that the problem is generally limited to generics sold to healthcare facilities through GPO contracts rather than directly to consumers through retail pharmacies.

Once all the GPO fees, together with production and distribution expenses get fully loaded into the cost, these drugs are often being sold with almost no profit margin. New and useful FDA authorities notwithstanding, the agency can't require a firm to keep making a drug that isn't profitable.

What about legislative fixes? "What we're trying to find out is whether there's a pattern behind the shortages that we can address," said Senator Richard Durbin. "We've got to get down to what is really behind it and try to solve it." Precisely.

The current House/Senate PDUFA negotiations are struggling with the issue of drug shortages.

On the House side the language requires the FDA to "*notify the Secretary of a discontinuance of the manufacture of a drug, or an interruption of the manufacture of a drug that is likely to lead to a meaningful disruption in the manufacturer's supply of the drug, and the reason for such discontinuance or interruption.*"

What drugs need to need to be reported?

*Drugs that are (1) life-supporting, life-sustaining or intended for use in the prevention or treatment of a debilitating disease or condition; and (2) not a radio pharmaceutical drug product, a product derived from human plasma protein and their recombinant analogs, or any other product as designated by the Secretary*

As you can see, the language is very vague as to what drugs fall into these categories and what, precisely, a "meaningful disruption" might be – and the Senate-side language is equally unclear.

Considering the high profile nature of this issue and the need for manufacturers to err on the side of both patient safety and legal prudence, this ambiguity will very likely lead to manufacturers reporting *everything* that could remotely lead to a shortage, thus exacerbating a signals-to-noise problem at an already over-burdened FDA.

Perhaps the best solution is for Congress to require the FDA to compile and publish a list of drugs that must be reported to the agency when circumstances leading to potential shortages arise.

This would allow companies to determine when they need to contact the FDA – and allow them to do so more swiftly and efficiently. Such legislative authority would also focus the FDA's energy on the most critical drug shortage situations – allowing them (with their limited staffing resources – it's worth repeating) to address them with greater skill and alacrity.

On the non-FDA side, Senator Orrin Hatch is focusing on the perverse economic incentives of Average Sales Price (ASP) as a key factor behind the problem.

His *Patient Access to Drugs in Shortage Act* is the only bill thus far dealing with the economic causes of drug shortages.

There are four key codicils:

1. **Price Stability** — The Hatch bill would change the Medicare reimbursement rate for generic injectable products with 4 or fewer active manufacturers from ASP + 6% to Wholesale Acquisition Cost in order to achieve market price stability.
2. **Medicaid/340B Rebate Exemption** — The bill exempts generic injectable products with 4 or fewer active manufacturers from Medicaid rebates and 340B discounts in order to achieve market price stability.
3. **Extended Exclusivity** — Manufacturers who hold an approved application for a drug that would mitigate a shortage can extend by 5 years any period of exclusivity, even if the drug is eventually moved from drug shortage designation.
4. **Drug Shortage Database** — The bill would allow the HHS Secretary to establish a mechanism by which health care providers and other third-party organizations may report evidence of a drug shortage.

Richard Feynman said, “The worthwhile problems are the ones you can really solve or help solve.”

Drug shortages are a worthwhile problem to solve – and we need to keep our collective eyes on the prize.