How the US Food and Drug Administration Can Solve the Prescription Drug Shortage Problem

Drug shortages are threatening care quality and cost-containment efforts. I describe the pharmaceutical marketplace changes that have caused the problem, and propose new policies to solve it, through changing incentives for producers and purchasers. I propose a grading scheme for the Food and Drug Administration when it inspects manufacturing facilities in the United States and abroad. The inspections' focus would change from closing unsafe plants to improving production process quality, reducing the likelihood that plants will be closed—the most frequent cause of drug shortages. (*Am J Public Health.* 2013; 103:e10–e14. doi:10.2105/AJPH.2013.301239)

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SHORTAGES OF PHARMACEUTICALS are suddenly occurring frequently in medical practice, and represent a bewildering situation for clinicians—one that most have never encountered. The shortages appear primarily among generic drugs, reliance on which is the main mechanism that health systems in the United States use to constrain pharmaceutical costs. According to the US Food and Drug Administration's (FDA's) report on drug shortages of October 31, 2011, the number of annual drug shortages had tripled from 61 in 2005 to 178 in 2010.[1] As of July 2012 there were more than 200.[2] What is it that has changed in the pharmaceutical market that has caused these shortages? What will it take to solve the problem? Once we better understand the underlying reasons for the shortages, remedies can be sought.

The shortages are occurring in all therapeutic categories. Although early reports noted the high incidence of shortages of sterile injectible drugs[3]—often those used for cancer treatment—subsequent observations have pointed out that the problem is far more widespread than that.[4,5] In fact, one report in 2008 studied the sudden shortage of heparin, the drug widely used for surgery patients.[6]

The shortages are the result of a sort of "perfect storm" involving 3 phenomena:

1. A consolidation of the market for generic drugs, with reduced numbers of both buyers and manufacturers;
2. An increased penetration of generic drugs in the overall pharmaceutical marketplace; and
3. An increased dependence on outsourced drug products, either chemical ingredients or manufactured drugs, coming from countries where inspections are more difficult to conduct.

Solving the problem will present difficult choices within our health system. The choices will be difficult because required changes will entail reordering priorities. For example, decreasing our reliance on generic drugs would reduce the enormous cost savings that generics have provided us. Increasing the number of competing generic firms and pharmaceutical purchasers would require far more aggressive enforcement of antitrust policies. Allowing the FDA more authority in overseeing shortages and regulating or redistributing production to alternative companies would expand the FDA's authority into uncharted areas. And more aggressive inspection of foreign suppliers to prevent contamination and other irregularities would raise the FDA's budget at a time of severe government attempts at cost constraint or (if the costs are passed on to manufacturers) raise the cost of many of our drug products.

BACKGROUND

The problem of ensuring an adequate supply of safe pharmaceuticals in the country is not new to the medical world but shortages have been gaining public attention. Recent articles by Jensen and Rappaport[7] and Chabner[8] have focused largely on oncology drugs. This was one of the findings, as well, of an international conference on drug shortages sponsored by the American Society of Health-System Pharmacists.[9] The FDA report, however, was helpful in documenting the increased breadth of the current problem.[10] The Assistant Secretary for Planning and Evaluation of the Department of Health and Human Services issued a recent *Issue Brief* that provided a more thorough economic analysis of the shortage problem.[11]

A common observation in the literature is poor communication between manufacturers and the FDA. The recommendations in the FDA's drug shortage report emphasize the beneficial role that improved communication between manufacturers and the FDA would have in letting the agency better anticipate the effect of supply disruptions. The thought is that if only the FDA were notified before an expected plant shutdown, alternative sources of production could be found. But a more careful study of the generic pharmaceutical market suggests otherwise. There are fewer producers than before that are manufacturing any particular product and there is little evidence that there is excess capacity that would allow a manufacturer to fill in when a competitor faced a shutdown. It is unlikely that the

drug-shortage problem can be solved without serious restructuring of the pharmaceutical industry and the way prices of drugs are determined.

The recommendation for improved communication with the FDA did appear to affect the legislative process, however. It resulted in a Presidential Executive Order in October 2011 urging pharmaceutical manufacturers to increase reporting of impending plant closures to the FDA so that the agency may be better able to prepare for shortages. In addition, there are 2 bills that have been introduced into the House and Senate—H.R. 2245 and S. 296—that would require manufacturers to notify the FDA of any discontinuance, interruption, or adjustment in the manufacture of a drug that may result in a shortage.[12,13] Currently, the only legal requirement for reporting a forthcoming closure to the FDA is if the company is the sole producer of a life-saving medication.

A remedy to the drug-shortage problem requires a better understanding of trends in the market for generic drugs in the United States. Three specific issues stand out: market consolidation, increased market penetration of generic products, and increased outsourcing of pharmaceutical components.

MARKET CONSOLIDATION

On the demand side, there has been consolidation among buyers of generic drugs. Competition among insurers has increased pressure to constrain health care costs—including the cost of pharmaceuticals. As the costs for new therapies rise, increased pressure is exerted on the costs of existing treatments, which include generic drugs. Insurers seek economies of scale and bargaining power by consolidating. One result is the growth of group purchasing organizations that attempt to reduce the price of drugs on behalf of many institutional buyers. Another part of the picture is subcontracting to organizations that can provide care more efficiently. This leads not only to growth of pharmaceutical benefit managers in the pharmaceutical sector, but also to programs offering clinical services such as behavioral health and even oncology treatment. As the number of purchasers of drugs falls, the pressure builds on individual producers to lower costs to the greatest degree possible, and profit margins fall.

On the supply side of the generic drug market, more and more pharmaceutical companies are merging and combining their resources to maximize their profits in an era of declining profit margins. Small generic manufacturers are combining to achieve economies of scale, and several of the larger research-oriented pharmaceutical companies have bought smaller generic manufacturers so that there are companies now that produce and market branded products in addition to producing and marketing generic versions of those brands. In other cases, pharmaceutical firms have begun to produce generic versions of their drugs directly, so-called "branded generics." This may lead to conflicts of interest, as firms will have an incentive to decrease generic production to shift demand to their more profitable branded products.

INCREASED MARKET PENETRATION BY GENERICS

Increased concentration in the generic pharmaceutical marketplace created by mergers and acquisitions of small generic manufacturers by larger ones leads to more aggressive price discounting and increased substitution of branded pharmaceuticals by generics to lower costs for health plans. According to the FDA, nearly 80% of prescriptions in the United States are now filled by generic drugs.[14] Product switching to generics following patent expiration used to be gradual, leaving branded pharmaceutical manufacturers with a "tail" of profit from branded sales. Today the switch to generics is rapid because health plans are competing to reduce overall health care costs. Consumers have become eager to switch to generics because they now face strong incentives in the form of lower copayments for generic products.

In addition, the scope of the generic market has broadened with the continuing introduction of major brand-name drugs that have either come off patent recently, or that expect to do so soon. This will further increase the generic share of the pharmaceutical market because the number of blockbuster drugs coming off patent appears to exceed the number being introduced.

The falling price of generic drugs can also be observed in the recent introduction of steep discounting by "big-box" retailers. Today more than 300 of the more popular, albeit older, drugs are already offered in very low-cost programs such as Wal-Mart's and Kroger's $4 generic drug plans.[15] This further increases the rate of generic penetration and broadens the generic role into a variety of markets. The result of the big-box stores offering low-cost generic drugs, perhaps as loss-leaders, is that pressure increases for other chain pharmacies to maintain their competitiveness by requiring reduced costs from their generic drug suppliers.

If this were not enough pressure to substitute generic products, there is yet another trend in the industry. Drugs that are not yet off patent are constantly under fire as patent challenges are becoming commonplace. The generic companies are gaining ground by trying to find loopholes and mechanisms that thwart patent protection, thereby increasing competition and lowering overall costs of the products.[16]

The popularity of biological (large molecule) drugs is increasing in the marketplace. Though some argue that biotech represents a safe harbor for pharmaceutical manufacturers seeking to avoid generic competition, the situation is changing. The European Medicines Agency approved a pathway for generic biological pharmaceutical product (so-called "biosimilar") approvals in 2005.[17] Though behind, the FDA has finally introduced its draft guidelines for biosimilar products, after it was charged with this responsibility in the 2010 Affordable Care Act.[18] Development and production of biological products is expensive, but the market for these products is large and growing, and so are incentives to reduce their cost—hence, the interest in biosimilars.

INCREASED PRODUCTION IN NONINDUSTRIALIZED COUNTRIES

Reduced profit margins of generics have created cost-saving incentives in the supply chain, leading to increased globalization of production and outsourcing. Falling prices and profit margins drive manufacturers to seek low-cost production sites. This

downward price pressure has led to outsourcing of drugs or chemical constituents—often from countries that have proven more difficult to inspect and ensure good manufacturing practice.

These trends have led to more complex supply chains for raw materials, active ingredients, and the manufacturing of final products. Off-shore sourcing frequently occurs in plants that have been more difficult for the FDA to inspect, which has led to production irregularities that have created product recalls and plant shutdowns. This was the problem behind the heparin recall and shortage of 2008. At the time, the active ingredient used by both of the manufacturers of heparin in the United States was produced in China, but the FDA did not then have a single Mandarin-speaking inspector in China.[19] Following public and political outcry, the FDA has become more stringent in its inspection regimen for foreign plants. Because single plants may produce more than 1 product or component, any interruption in the supply chain may have a multiplied effect by disrupting the supply of several drugs.

LOW INVENTORIES

These developments of market concentration, reduced profit margins, generic penetration, and outsourcing would not, by themselves, make the generic drug industry more vulnerable to shortages, except for their effect on producer inventories. The producer of any profitable product has an incentive to hold inventory to protect against lost sales caused by supply interruptions. Why does this process not work in the case of generic drugs? If producing generic drugs generates profits, then producers would be expected to hold inventories that would be sufficient to ride out production stoppages. The trouble is that holding inventory costs money—in lost sales (especially for products with limited shelf-life) and storage costs. It is these costs that are compared with the benefits of inventory, based on the protection against lost profit resulting from a supply disruption. Any producer must decide on the amount of inventory to hold, based on the costs of inventory and the value of lost sales that the inventory would protect against. We have seen that, for several reasons, profits from generic drug production are smaller than they used to be. If profits are low, the costs of inventory loom large and the burden of lost sales is less serious. Therefore, inventories of generic drugs are likely to be smaller than they used to be, so that when supply interruptions occur (and they are expected to do so more frequently), shortages will be felt more immediately at the retail level.

It is thought by some that the shortage problem could be solved if only firms were less secretive toward the FDA with respect to plans to close plants, or if the FDA could only share information about prospective shortages with other manufacturers, or if physicians and patients knew about impending plant closures earlier so that drugs could be chosen that were not affected by imminent plant closures. But the cause of the problem is not insufficient information sharing among firms, the FDA, and consumers, as has been suggested in the literature. The cause is, rather, insufficient inventories to protect the supply chain from disruptions—and these insufficient inventories are the direct result of falling generic profit margins.

A REMEDY FOR IMPLEMENTATION BY THE FDA

Currently, the incentive on the production side is to produce a product as inexpensively as possible without having production shutdowns. If profits were low enough and the likelihood of being inspected and "caught" producing unsafe products were low enough, it could be a profit-maximizing strategy to produce just at, or even below, the minimum acceptable level—and accept the consequences (as rarely as they occur) as another cost of doing business.[20]

The FDA inspects plants in the United States and abroad regularly and uses its authority to close a plant that has serious safety hazards. These inspections could do much more to create incentives for manufacturers to improve product quality—if the inspections were done differently.

The all-or-nothing drug inspection policy is similar to the way inspections of restaurants used to occur: restaurants that were safe enough were allowed to remain open, whereas those scoring below the passing level were immediately closed pending repairs and re-inspection. In 1998, Los Angeles County adopted a different approach—of giving letter grades to restaurants, rather than simple "pass/fail" determinations.[21] The county's Department of Public Health has found that consumers are sensitive to letter grades and restaurant owners have found that they had an incentive to maintain an "A" grade, rather than let it slip down to a "B" grade (oral communication with Jonathan Fielding, director, Los Angeles County Department of Public Health, November 15, 2009). This approach has been copied by other cities, including New York.

For pharmaceutical plants, FDA inspectors could assign a numerical value to the safety of the manufacturing process and perhaps a letter grade. The new grading scale might have 4 designations, one for the highest quality, one for a lower quality, a third that is a "barely pass" (that would allow production to continue on the contingency that certain practices will be improved within a specified timeframe), and a fourth grade that would automatically shut down production for fear of unsafe production standards. The grades would then become public knowledge. Distributors, wholesalers, and retailers would know a manufacturer's grade.

The grade would have 2 effects. First of all, it would serve as a warning to producers that a barely passing grade means that the plant is in jeopardy of failing inspection the next time. In addition, a low (or declining) grade would also serve as a warning that might have economic consequences for the firm, depending on the quality sensitivity of its purchasers. One might imagine a scenario in which an insurer offers subscribers a guarantee that all of its pharmaceuticals (from wherever they are made) are from "A"-graded plants. Assigning a grade will have to take account of the complexity of the drug supply chain, in which the active ingredient may originate in one plant, other chemicals in another, and the final manufacturing takes place in still another site. Perhaps some consumers would be willing to pay more for this assurance that they are avoiding products with a higher likelihood of being unsafe. On the other hand, another insurer might feel that its consumers would not be willing to pay more for products from the

"A"-designated plants, and it would purchase "B"-quality drugs—or even "C"-quality inputs, and demand commensurately lower prices. This would create an incentive for some manufacturers to produce a higher-quality product. Furthermore, warning manufacturers that production quality is near the shutdown stage offers an opportunity to improve quality before the next inspection and avoid a future plant closure.

EFFECT OF FDA GRADES ON DRUG QUALITY AND PLANT CLOSURES

There is presently no information on whether consumers and their health plans are price-sensitive to quality differences in the manufacture of pharmaceuticals, and what effect such price sensitivity has on quality of producers, because quality differences are currently unknown outside of the FDA and the manufacturer.

Though limited, there is some direct evidence that consumers of pharmaceuticals are sensitive to quality. Drug prices have been shown in hedonic analyses to be related to 3 dimensions of quality—efficacy, safety, and convenience—demonstrating in a broader context the notion that drug purchasers are willing to pay more for drugs that are more effective and less risky.[22] These studies, however, have not yet looked at the quality of the manufacturing processes.

Though we have no direct evidence on the effect of pharmaceutical manufacturer grades on either consumer or provider behavior, there is considerable evidence in other settings that suggests that a grading scheme such as that proposed will produce favorable results.

Devin Pope observed that hospital rankings published by *US News and World Report* were influential in changing consumer behavior, as they affected hospital admissions and revenue in the expected direction.[23] Pope stated, "Academic research has shown that in a variety of situations, rankings can have a significant input on consumer decision making."[24] As mentioned, the hospital quality ratings studied by Pope are not, literally, grades.

Quality assessments in industries outside health care have also been shown to influence both consumer and producer behavior. Restaurant grading programs, as noted previously, have been popular with consumers and evidence suggests that they have increased consumer sensitivity to grades, induced restaurants to improve their quality of food preparation, and reduced the incidence of food-borne illness.[25]

In a wide range of other industries, *Consumer Reports'* evaluations of consumer products have been very influential in directing consumption toward highly rated products, demonstrating that in many areas of consumer goods consumers are sensitive to quality differences.

The price sensitivity of consumers to FDA quality ratings for pharmaceuticals is probably not a simple relationship. The willingness of consumers to pay more for higher quality drugs depends, for example, on the range of quality options available. If one product has an "A" rating, and the other products have a "C" rating, consumers might feel that the "A" product is worth a higher price, but if there is a "B" product available, perhaps many will feel that "B" is "good enough." The source of the ratings is important as well. When the FDA issues drug quality ratings, consumers will be more likely to trust the assessment than they would an industry rating program. The nature of the drug is also important. A rating difference for a life-saving drug would be expected to be more important than a similar rating difference for a less essential product.

CONCLUSIONS

Shortages of generic drugs are highly disruptive to the health system, causing both dismay and consternation among patients, their physicians, and health plans. The costs of supply disruptions can be considerable. They include wasted money resulting from the substitution of more expensive drugs for the drugs originally ordered; the time costs as physicians, administrators, and patients search for elusive products; and the medical harm caused by a system's inability to administer a required drug, or the misuse of a less well-understood replacement drug. Although the initial extent of the problem was thought to be limited to a particular class of drugs, the problem has spread more widely and has grown in extent.

Initial ideas were that the problem was attributable to ineffective supervision by the FDA, caused by lack of information from manufacturers who were facing imminent plant closures. And some recommendations have suggested that the FDA might relax some production standards when faced with a production shutdown.[26]

The underlying reasons for the shortages lie deeper than these ideas suggest. The problem is caused by incentives brought about by greater competition and market concentration among generic drug producers and purchasers, the increased role of generic drugs in the US health care system, and increased reliance on outsourced production to plants that are inherently more difficult for the FDA to supervise. All of these factors lead to reduced product inventory held by manufacturers, who are facing an increased likelihood of needing to use that inventory to continue sales during periods of supply disruptions.

A remedy for the problem would be a revision in the way that the FDA inspects and grades drug production facilities. The new system, by using a grading scale, rather than a simple pass–fail result, would provide notice to manufacturers and their customers when production quality was excellent, or was declining. It would create an incentive on the part of producers to actually improve the quality of production to receive a higher grade, and, hence, a higher price. And it would give an opportunity for manufacturers to improve their production processes so that they would not "fail" the next inspection. There is no guarantee that a -grading scheme would improve production quality and reduce the number of plant shutdowns, but the attempt is perhaps worth trying. ■

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Human Participant Protection

Human participant protection was not needed because human participants were not involved in the study.

Endnotes

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20. This is analogous to a motorist who routinely drives faster than the speed limit because the time savings are worth more than the cost of the rare speeding ticket.

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26. Some policy discussion has suggested that the FDA might relax some production standards when faced with a production shutdown. For example, a proposal has been made that some shelf-life standards could be relaxed without harming patients. This suggestion surely takes one onto a slippery slope in terms of standards enforcement. None would argue that standards that were unrelated to product quality and patient outcome should be eliminated. This has nothing to do with product shortages—it is merely an example of an unnecessary regulation. But if the recommendation is that useful standards regulation should be relaxed in times of a shortage, then another concern arises. The implication is that access to lower-quality (less-useful) drugs is, somehow, preferable to reduced access to full-quality products. Many consumers would chafe at having to make such a severe choice.