5 Questions: Link on recent shortages in cancer-drug supply

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In February, the United States came within weeks of running out of preservative-free methotrexate, a generic drug that is an essential component of chemotherapy treatments for the most common childhood cancer, acute lymphoblastic leukemia. The crisis put hundreds of children's lives at risk in a troubling way: Oncologists know how to save the lives of most of these children, but can't do so without the drug. Sadly, the methotrexate shortage was not unique; in the last five years, drug shortages have escalated in a variety of medicines. Chemotherapy shortages, however, are generally more critical because there are no equivalent alternatives for most of these medications.

Pediatric oncologist Michael Link, MD, who has treated children with cancer at Lucile Packard Children's Hospital and Stanford Hospital for more than 30 years, is currently the president of the American Society for Clinical Oncology. During his term, he has vigorously advocated for regulatory changes to prevent drug shortages. Science writer Erin Digitale worked with Link to explain the shortages in this "5 Questions" piece, which was adapted from a commentary article he co-wrote for the March 1 issue of the *Journal of Clinical Oncology*.

Q: What role do economic factors play in the shortages?

Link: I think the unifying mechanism behind the drug shortages can be traced to simple economics. First, some basic market dynamics are at

play: Manufacturers have little incentive to make drugs with low profit margins and often shift their resources to drugs for which higher profit margins are anticipated. The vast majority of chemotherapy drug shortages have been in sterile, injectable, generic agents, most of which are relatively inexpensive. Four drug companies account for more than 70 percent of the generic chemotherapy market; if one company experiences an expensive breakdown in a single piece of drug-manufacturing equipment, that may shift the company's interest to a more lucrative product, triggering a drug shortage.

Q: In addition to those basic market factors, some people have suggested the Medicare Modernization Act is partly responsible for drug shortages — and the timing is certainly suggestive, since chemotherapy shortages began escalating within a year of the law's 2005 implementation. What do you think?

Link: I agree that the Medicare reimbursement system is partly to blame. In Europe, where there is no equivalent system, prices of generic drugs are higher than in the United States, and the prices of brand drugs are lower (because of agreements between drug companies and governments). This maintains a reasonable profit margin for generic drugs, allowing competition to continue and largely preventing drug shortages.

In the United States, Medicare caps at 6 percent the amount over the average sales price that it will reimburse physicians for drugs used in their practices. Because of the way Medicare calculates the average sales price, there is a six-month lag between the time manufacturers submit their price data and when changes in prices are reflected in reimbursement. This makes it difficult for manufacturers to raise prices,

creating a situation in which — for low-cost drugs with dwindling profit margins — there is little incentive to continue production.

Q: What kinds of problems contribute to shortages on the drug manufacturing side?

Link: Drug companies have pointed to contamination of and shortages in the supply of raw materials and shutdowns of plants by the FDA for quality-control issues. According to the FDA, manufacturing and quality issues account for more than 50 percent of shortages, with shortages of active pharmaceutical ingredients accounting for only 5 to 10 percent of the problem. In addition, in Congressional hearings, representatives of generic-drug companies have pointed to FDA regulatory complexities and burdensome administrative requirements to recertify the manufacturing of generic drugs. Others have cited consolidation within the pharmaceutical industry, resulting in fewer companies willing to produce generic drugs.

Q: How is the so-called “gray market” involved in drug shortages?

Link: The shortages have created an opportunity for secondary drug distributors to make additional profits. With early knowledge of potential drug shortages, they have hoarded chemotherapy drugs in anticipation and sold them at amounts that are 650 percent to 3,000 percent of the original prices. This activity, referred to as a gray market, is actually a form of price gouging. The gray market has raised additional concerns about the reliability of drugs being sold to practices, because the pedigree of the drugs is uncertain. There is limited to no ability to trace their chain of custody, nor can we be sure they have been handled, stored and transported as required. It is estimated that the gray market accounts for up to 50 percent of drug sales during a drug

shortage.

Q: What can be done to alleviate the problem?

Link: In November, President Obama issued an executive order calling for the FDA to broaden reporting of potential drug shortages, hasten the review process to better prevent or respond to shortages, and work with the Department of Justice in cases of possible drug price gouging or stockpiling.

For the future, establishing a price floor for generic chemotherapy drugs is one option. Many of these drugs are now so inexpensive that, unless something changes, they will never be profitable to manufacture. (For instance, the average price of a vial of carboplatin is less than $5.) Minimum prices for generics could be based on some comparison with a similar brand drug, perhaps by pricing the generic at 5 to 10 percent of the price of the brand drug. This could provide incentive for generic drug companies to remain in, or enter, the market. Although some experts worry about increasing the cost of care, it is worth noting that continued drug shortages already cost an estimated $200-$300 million per year.

Another potential solution — mandatory reporting legislation, which would require manufacturers to provide the FDA with six months notice of anticipated drug shortages, — is now pending in Congress. Some worry that this would exacerbate hoarding. However, much of the mandated communication would be confidential, allowing the FDA to take steps to mitigate the problem without publicizing it. In any case, the proposed legislation has not moved forward. I understand that other legislative initiatives are under development.

Speeding up FDA approvals for generic drugs could also help. There is now a backlog of more than 2,000 unapproved generic applications, with

a median time to approval of 30 months. It would be especially valuable if new applications for generic drugs could complete FDA review within three to six months of an announced or impending drug shortage.

In terms of American lives, a solution to the problem is priceless.

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