

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## The Generic Drug Shortage

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**H&O** What are some of the issues surrounding generic drugs in oncology, and what has led to this drug shortage?

**GT** In the early 1980s, the generic drug industry underwent a massive legislative overhaul in what is now called the Hatch-Waxman legislation. It was a fairly broad legislation, with 2 components: one that concerned clarification and changes in patent law, and another that enacted legislation making it easier for generics to enter the market. As a result, generic drugs came on the market faster, there was more competition, and the prices for these drugs dropped more rapidly. These were all advantageous for the consumer, initially. However, the drug prices decreased so much that they were barely above the cost to manufacture them. The margins came down significantly. Oftentimes, if a brand-name drug with a higher profit margin is available, manufacturers will stop producing its generic.

Subsequently, there has been a whole host of other generics that have come on the market, such as the cholesterol-lowering pill known as Lipitor. The price of Lipitor decreased by more than 90% in 2 weeks because of generic competition. This means that the manufacturing capacity for these manufacturers is being taken up by other drugs. These factors have led to the industry being consolidated into a few companies that manufacture generic drugs. Recently, the US Food and Drug Administration (FDA) has increased their quality control and scrutiny of these manufacturers, and plants have been closed.

The shortage of oncology drugs can be attributed to several reasons. Manufacturers tend to avoid oncology drugs because they are the hardest to produce. Oncology drugs are often intravenous and thus require sterilization,

unlike oral drugs. These drugs are dangerous and cytotoxic, so their manufacturing facilities must sometimes be segregated from all other non-oncology drug facilities. Oncology drugs are the hardest to create, demand the most out of the facility, and cost the most. However, they return very little because they are relatively low volume compared to agents like Lipitor or antacid drugs. In addition, agents like Lipitor or antacid drugs can be replaced with similar drugs, whereas there are no substitutes for oncology drugs.

**H&O** What have been the implications of the drug shortage for patients, research, and hospitals?

**GT** Patients are experiencing delays in their therapy, research protocols are being delayed in recruiting patients, and hospital pharmacists are wasting an enormous amount of time searching for drugs. Imagine the issue from a patient perspective. You have been diagnosed with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), and are told by the doctor that the cure rate is quite high, provided that a very specific sequence of events is followed as part of your treatment. You return to the doctor after 3 weeks, expecting more chemotherapy, but the doctor tells you that the drug is not available because manufacturers are not making enough of it, if any. This is a very devastating set of events. It is especially frustrating for patients with leukemia, one of the most curable forms of cancer.

From a research perspective, many centers and protocols have had to delay patient recruitment because of the lack of oncology drug supply. For example, a patient with AML who has relapsed after the first round of treatment is advised to go to a major cancer research center and enter into a clinical protocol. However, the research center must turn the patient away because it does not have the proper drugs. The drug shortage is delaying clinical

trials in many different types of cancer, including breast cancer, leukemia, and sarcoma. It has a massive impact on all of our research. Not only does it affect the patient and researchers, it also impacts everyone down the line because the research done now is supposed to guide us to better therapy throughout the next 3–5 years.

Hospitals are also affected. An article by the American Society of Health-System Pharmacists (ASHP) reported that some hospital pharmacists must spend 25–40% of their time dealing with the shortage. They are on the phone with the distributors, manufacturers, and other pharmacies, trying to find drugs. This shortage is impacting everyone.

### H&O What has been done to combat the issue?

**GT** In November 2011, President Obama signed an executive order making this issue a priority for the FDA. I believe the FDA is doing whatever it can to combat this issue. The FDA has a dedicated drug shortage group; in my personal experience, this group has been enormously responsive in trying to help. However, they must adhere to regulatory and legislative limitations, such as ensuring the quality of the drug supply. They are trying to expedite reviews of new applications from new manufacturers. There have been several cases where they have worked with manufacturers to import drugs that are not available in the United States. The FDA is working with these manufacturing companies to ensure that the foreign drugs meet our quality standards, and can then be brought into the country. I was directly involved in one of those importations, in which I negotiated with the FDA on the European drug levoleucovorin, and the FDA was exceptionally cooperative.

### H&O Are there any legislative changes that should be made?

**GT** I think that the only potential fix is one of price control. There are now legislative limitations on the pricing of these drugs. There are limitations on how high the prices can rise and how much a physician can charge above the average cost. It has been speculated that if this price control were loosened for generics, more supply would come onto the market. It might also be helpful to shorten the time-frame during which the FDA reviews applications from new generic drug manufacturers. The statutory time the FDA currently has to review an abbreviated drug application—which pertains to a generic drug—is 18 months. For a new drug that is not generic, the review time is only 10 months. There could be an update that says if the drug is in short supply and is life changing, the FDA must review it in 6 months. They already take this approach for new oncol-

ogy drugs that are intended to fill an unmet need, when no other alternatives are available. This could be extended to generic drugs that are life saving and in short supply.

### H&O What are the impediments to the development of generic drugs in oncology?

**GT** It takes approximately \$1.5 million to bring a drug to market. After review by the FDA, the total time in development is approximately 2 years. In addition to those obstacles, there is an uncertain market ahead, because it is possible that the shortage might be over by the time approval is granted. There may be other competitors as well, and the chance of recouping all of the money spent is very small.

### H&O What is the purpose of the Citizen's Oncology Foundation?

**GT** We are still in the formation process, but the Citizen's Oncology Foundation is a group of dedicated oncologists who have more than 200 years combined experience in oncology drug development. We are committed to helping provide access to life-saving medicines that are not universally available right now. Interestingly, this drug shortage is not a problem in Europe. We have identified suppliers in Europe with drugs that we believe meet all of the quality standards of the US drugs. These are fairly simple agents that do not differ much from US drugs. They just need to be manufactured at a facility approved by the FDA. Thus, we are working with suppliers in Europe to import drugs as needed into the United States in order to fill critical demands. The impetus for our work is that we want patients to have drugs, and we want clinical trials to move ahead. We believe we can raise money through charitable contributions and philanthropic donations. If it turns out that we are not needed, that is perfectly fine. It is still a victory, because the patients will have the drugs they need to improve, and possibly save, their lives.

### Suggested Readings

US Food and Drug Administration. Current Drug Shortages. <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm>. Accessed January 26, 2012.

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*Dr Tidmarsh is the Chief Executive Officer at La Jolla Pharmaceuticals, Inc., the Executive Director at Anavex Life Sciences, and the Owner of BioMedical Drug Development.*