Major Setback in US Cancer Drug Shortage ***(courtesy: Medscape Medical News. 10/18/2013)***

The already small number of producers of generic cancer drugs in the United States just got smaller.

Ben Venue Laboratories, a major manufacturer of generic chemotherapy injectables, announced the closure of its plant, in Bedford, Ohio, earlier this month, citing problems with both the facility and projected revenues. It will effectively depart the US market by the end of the year.

The loss is a significant blow to the recovery of the US marketplace for generic cancer drugs, said Erin Fox, PharmD, director of the drug information service at the University of Utah Hospitals and Clinics in Salt Lake City. Dr. Fox has been monitoring drug shortages in the United States since 2001.

"I really feel like it's a big step back," she told *Medscape Medical News* in an interview

The US market for generic cancer chemotherapy injectables has improved since the "crisis" of 2011, she said. But the loss of Ben Venue, which a company Web site touts as "one of the largest sterile injectable facilities in the world," is important. "Our supply chain is that much more fragile with the closing," said Dr. Fox

"A significant portion of the ability of the market to meet demand is now gone," said William Greene, PharmD, chief pharmaceutical officer at St. Jude Children's Research Hospital in Memphis, Tennessee, who also spoke to *Medscape Medical News* about the Ben Venue closure.

"We are reaching a scary situation," said Sara Butler, PharmD, oncology clinical pharmacy supervisor at Barnes-Jewish Hospital in St. Louis, Missouri, about the loss of manufacturing capacity in an interview.

Another expert said that the impact of the plant closure is unclear.

"There's not enough transparency [from product distributors about the factory origins of generic drugs] to know exactly what [Ben Venue is] producing at this point," said Jeffrey Ward, MD, from the Swedish Medical Center in Seattle, who is chair of the Clinical Practice Committee of the American Society of Clinical Oncology (ASCO). "That's almost scarier than knowing what the impact is," he told *Medscape Medical News*.

Set Back of 4 to 6 Years

Before the news of the Ben Venue closing, Dr. Fox believed that the problem would see a significant improvement in ongoing and active shortages in about 2 years. Now, that time period doubles or triples. "I think it does set us back 4 to 6 years," she said.

Dr. Fox's speculative timeline was revealed earlier this week in the trade publication *The Cancer Letter*.

Ben Venue, which specializes in making injectable drugs, has been a major player in the US market for generic chemotherapy, Dr. Fox explained. There is no new manufacturer to take Ben Venue's place. "Nobody's jumping on board right now," she said.

In the US cancer generics market, there are 3 "workhorse companies" that provide most of the generic chemotherapy injectables, said Dr. Fox. These are Hospira, Teva, and Bedford Laboratories, which is a distributor of Ben Venue products and products of other third parties. (Bedford and Ben Venue are both owned by Boehringer Ingelheim.) Pfizer is also in the market. Given this small circle, the loss of Ben Venue's manufacturing is significant, she believes. "We really need another supplier [of generic oncology products]," she said.

However, she emphasized that the situation is not as bad as it was 2 years ago. "People are not going without treatment, as in 2011."

A different opinion comes from Dr. Butler, who said that at Barnes-Jewish Hospital, there are still times when staff have to tell cancer patients that "we don't have certain drugs." She believes the situation has become "much worse in the last 2 years."

New Data on Chemotherapy Shortages

Currently, there are 31 cancer drugs actively in short supply, which is down from nearly 40 in 2011, according to Dr. Fox.

Also, there were only 4 chemotherapies that newly went into shortage in 2013, compared with 26 new chemotherapy shortages in 2011, according to data from a presentation that Dr. Fox made this week at a conference of hospital executives in Atlanta.

However, c Notably, Ben Venue played a role in the cancer drug shortage crisis of 2011, Dr. Fox believes.

The production facility closed that year after a series of customer complaints about products and inspections from the US Food and Drug Administration (FDA) and other agencies. Subsequently, 2 very important mainstays of cancer treatment — doxorubicin and methotrexate — went into extremely short supply, said Dr. Fox. It turned out that Ben Venue was a producer of both drugs.

The marketplace eventually reacted, with some help from the FDA, and both dire shortages were alleviated.

Among other events, the FDA approved APP Pharmaceuticals as the manufacturer of a preservative-free form of methotrexate, and allowed an Indian manufacturer, Sun Pharma Global, to export generic doxorubicin to the United States.

After the 2011 closing, the Ben Venue plant resumed "limited" production in 2012. By that time, the drastic impact of the initial closure on the marketplace had passed, said Dr. Fox. "All of that pain has been dealt with in one way or another," she explained, adding that it holds true today, even with the news of the plant closure.

Immediate Problems

The closure nonetheless creates immediate clinical problems. For instance, Ben Venue and its sibling company, Bedford Laboratories, have been the sole US suppliers of thiotepa, Dr. Fox pointed out. The FDA is now allowing thiotepa, which is used in stem cell transplants and other settings, to be imported from Italy. "But that's very inconvenient for people; there's almost a month's delay," she said.

Dr. Greene said that procuring thiotepa from abroad is "exceedingly expensive and time consuming," and that St. Jude's is now looking for alternative drugs for chemotherapy regimens involving thiotepa. He is also concerned that daunorubicin, which is used in the treatment of leukemias, will fall into short supply because, now, only Teva will be producing the drug.

The Ben Venue plant has also been the world's sole manufacturer of *Doxil*, the branded version of doxorubicin hydrochloride liposome injection, which is owned by Johnson & Johnson. The product could disappear from the market for a time until a new manufacturer is found, as reported this week by*Medscape Medical News*.

Currently, Doxil is being evaluated in a number of clinical trials. Its potential disappearance from the marketplace puts the viability of these trials at risk because a generic substitution, which would be acceptable for patients in the clinic, is not possible in a research setting, ASCO's Dr. Ward pointed out.

The Murky World of Generics Manufacturing

Dr. Ward said he was surprised to learn that a branded drug, Doxil, owned by a major drug company, Janssen/Johnson & Johnson, was made by a generics manufacturer. But the cancer generics market is full of surprises and unknowns, he noted.

Take the example of Bedford Laboratories, which began as a division of Ben Venue in 1993. Both entities have been properties of Boehringer Ingelheim since 1997.

Unlike Ben Venue, Bedford will remain in business.

That's good news, because Bedford is the leading provider of cancer generic sterile injectables in the United States, with 30% of the market, according to an analysis led by Janet Woodcock, MD, head of the pharmaceuticals division at the FDA, and published earlier this year (*Clin Pharmacol Ther*.2013;93:170-176).

But currently, Bedford is "out of stock" of a long list of sterile injectables, including many oncology products. The list, posted October 1 on the company Web site, includes Adriamycin, cytarabine, dacarbazine, etoposide, gemcitabine, methotrexate, paclitaxel, and vinblastine.

Some of these are very important products, said Dr. Ward. For instance, gemcitabine is part of the standard of care in pancreatic cancer.

"What you don't know from that list is how many of these drugs were manufactured by Ben Venue and how many come from elsewhere," he explained.

The company product announcement says these out-of-stock injectable drugs could be available "pending production as capacity permits."

"Bedford will continue to distribute products manufactured by Ben Venue Laboratories until that inventory is depleted," a company spokesperson said in an email to *Medscape Medical News*.

Generally, "there is not much transparency in this market," observed Dr. Ward.

He explained that producers of generic sterile injectables in the United States are regulated in terms of original licensure and the design of manufacturing processes. "But the FDA does not know who is having problems with a factory or profitability," he said, referring to the 2 reasons cited by Ben Venue for leaving the US market.

Generics companies can also switch their manufacturing from a drug that is not profitable to one that is, which can play havoc with the market availability of agents, said Dr. Ward.

He noted that the generics market, which includes chemotherapy injectables, is inherently volatile because profit margins are thin. Once on the market, "generics get very cheap very quickly," he said. Any variable that increases costs cuts into these already thin profits. This is exacerbated by that fact that the Centers for Medicare & Medicaid Services only updates the stated average sales price every 6 months, forcing companies to wait long periods for an approved adjustment in price. As a result, companies can feel a need to start and stop the production of certain products.

St Jude's Dr. Greene agrees that the generics market is a murky business in which many manufacturing and related planning details are not disclosed. "We just know when something is gone," he noted. The FDA Safety and Innovation Act, enacted in 2012, requires that drug manufacturers to notify the FDA as soon as they anticipate interruptions in drug production, and 6 months in advance if a product is to be discontinued. Although the law "improves the situation," Dr. Greene said, it has shortcomings.

Dr. Ward observed that the generics manufacturers managed to retain a number of loopholes in the law, which weaken its sentinel nature.

Seven companies supply 90% of the generic injectables market, said Dr. Fox. However, not all 7 make oncology products. Who manufacturers what product at what time is not publicly available information, and must be discerned through data detective work, she said.

The whole model is problematic, said Dr. Ward. "We have left it to business to ensure our drug supply."

Chemotherapies in short supply are just a small part of the overall drug shortage picture in the United States, Dr. Fox pointed out.