

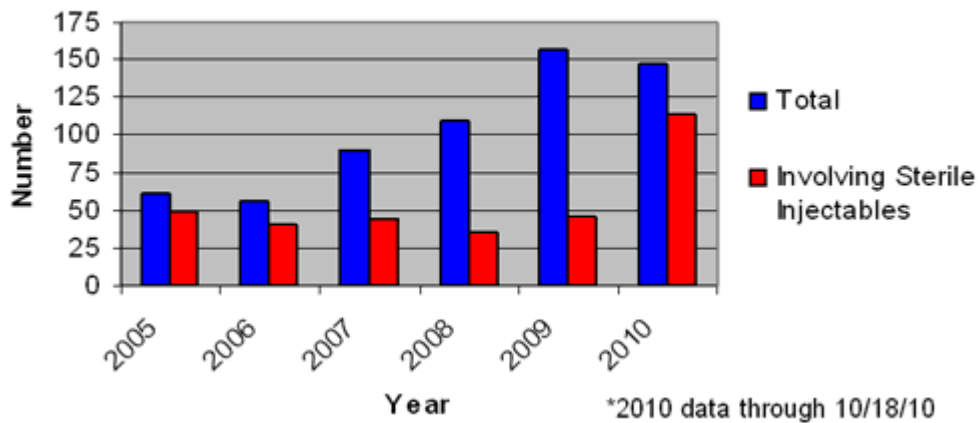
## Continued Shortage of Chemotherapy Drugs Causing Concern

A serious shortage of commonly used chemotherapy drugs that began several years ago and worsened in 2010 is taking a toll on medical facilities and causing concerns among patients and doctors alike, according to representatives from government and professional groups. The continued shortfall is part of a more widespread shortage of drugs, including those frequently used in anesthesia and to treat dangerous infections, and has raised anxiety about patient care and clinical trials in which the drugs, many of them generic, are important components of treatment.

"We've heard a crescendo of complaints and concerns," said Dr. Michael Link, a pediatric oncologist from the Stanford University School of Medicine and president-elect of the American Society of Clinical Oncology (ASCO). It's not possible to quantify the extent of the impact on patient care, Dr. Link noted, but, based on what's known, "it's the worst shortage we've experienced in three decades. In terms of scope, it's huge."

All of the chemotherapy drugs involved in the shortage are in a category known as sterile injectables, explained Valerie Jensen, associate director of the [Drug Shortage Program](#) in the FDA's Center for Drug Evaluation and Research. Sterile injectables, in fact, account for 77 percent of the overall shortage.

### U.S. Shortages



Although drug shortages in the United States have continued to worsen over the past 4-5 years, the number of sterile injectables in short supply—particularly common chemotherapy drugs—increased dramatically from 2009 to 2010. (Data courtesy of FDA's Center for Drug Evaluation and Research)

Although production and quality issues have been chief reasons for the shortage, the problem can also be traced back to the business realities of manufacturing pharmaceuticals, Ms. Jensen explained via e-mail. This is particularly the case for sterile injectable chemotherapy drugs.

She explained that there used to be an adequate number of manufacturers for many of these sterile injectable drugs, but in recent years many of these companies have opted to stop producing the drugs "in favor of newer, more profitable products," Ms. Jensen continued, "since firms have a limited number of production lines and can only make a certain number of products on the lines they have."

For example, although eight companies had approval to produce [leucovorin](#) at one point, until very recently only two companies were still manufacturing the drug. The FDA recently granted another company approval to begin producing leucovorin, Ms. Jensen noted.

### Cooperatively Tackling the Problem

In November, spurred by the extent of the problem and the lack of any relief in sight, ASCO co-sponsored a meeting with the American Society of Health-System Pharmacists (ASHP), the Institute for Safe Medication Practices (ISMP), and the American Society of Anesthesiologists to analyze the causes of the shortage, how best to address it, and how to prevent or mitigate such problems in the future. Officials from NCI and the FDA—who, like officials from ASHP, are closely tracking the shortage and have a [Web site](#) that is updated daily with new information on the status of the drugs in short supply—attended the summit. A [report](#) of the proceedings was released on January 10.

In the meantime, medical facilities and providers are doing their best to deal with the shortages. It's

clear, however, that the situation is taking a toll, particularly on smaller practices and centers. According to an [ISMP survey](#) of 1,800 health care professionals conducted in September, the risk of medical errors is on the rise as hospitals and other health care facilities cope with issues such as dosing or frequency of administration when forced by the shortage to use alternative drugs. More than one-third of respondents said the shortage had led to a medical error that could have harmed a patient.

For example, the drug [etoposide](#), which is used to treat a number of cancers, including lung cancer, has been in short supply on and off for nearly 2 years. Of the four companies that manufacture it, only one has been able to cite a reason—manufacturing problems.

Typically the intravenous formulation of etoposide is preferred, explained Dr. Ali McBride, a clinical oncology pharmacist at Barnes-Jewish Hospital in St. Louis. Because of the shortage, however, oncologists frequently have been forced to resort to the oral formulation, “and that has led to dosing problems,” Dr. McBride said. Etoposide is also used for patients who undergo hematopoietic stem cell transplants, including children. In several cases, Dr. McBride said, treatments had to be delayed because the drug wasn’t available.

The shortage of two other commonly used chemotherapy agents, [doxorubicin](#) and [cisplatin](#), is also emerging “as a real problem,” said Dr. Link. “Doxorubicin is very widely used, so the impact is enormous,” he continued, particularly because of a number of diseases, such as metastatic breast cancer, sarcomas, and lymphomas, doxorubicin is a mainstay of treatment. “Clinical trials have shown it to be a major part of the improvement in outcome,” he said.

With cisplatin, the biggest concern has been in testicular cancer, where its use is directly related to the extremely good survival rates seen with chemotherapy. The alternative, [carboplatin](#), “lowers the cure rate in young men with testicular cancer by 10 to 15 percent,” explained Dr. Lawrence Einhorn of the Indiana University School of Medicine in a recent [ASCO interview](#).

If a drug is in very short supply, it is typically reserved for patients who stand to benefit the most. In most cases, Dr. McBride said, “the priority is patients for whom the therapy is curative.”

The shortage’s impact on medical facilities appears to vary by facility type, noted Bona Benjamin, ASHP’s director of medication-use quality improvement. “Organizations like ambulatory infusion centers that don’t have the usage volume of large hospitals may receive proportionately less drug,” she explained, so some of them are feeling the shortage more acutely than larger medical centers.

### Impact on Clinical Trials

Cancer clinical trials are also being affected by the shortage, although the full extent of the impact is unclear. NCI has been advising its clinical trials cooperative groups on how to proceed when a drug that is part of a treatment protocol is in short supply or not available at all.

“The highest priority when shortages occur is to ensure that all patients currently enrolled in the trial are treated appropriately,” explained Dr. Margaret Mooney of NCI’s [Division of Cancer Treatment and Diagnosis](#). Federal regulations allow for trial leaders to deviate from the research protocol to ensure patient safety if there is an immediate hazard, such as when an essential component of the protocol therapy is not available. Those treatment modifications must be documented and communicated to the study patients and the Institutional Review Board (IRB) overseeing the trial, Dr. Mooney said.

For new patients, she continued, trial sites must work with their local pharmacists to determine if they expect to have an adequate supply of the agents being used in the trial. If they don’t, accrual of new patients is temporarily halted. In cases where a shortage is expected to be prolonged, investigators may amend trial protocols—with IRB review and approval—when there are acceptable alternatives. That is handled on a trial-by-trial basis, Dr. Mooney said.

“It’s not a crisis, but we certainly have felt the effects,” said Dr. Jan Buckner of the Mayo Clinic and chair of the North Central Cancer Treatment Group (NCCTG). The cooperative group hasn’t been forced to stop any of its trials because of the shortage, Dr. Buckner noted, “but we have had to identify alternative regimens that we felt were therapeutically equivalent.”

The shortage has also forced NCCTG to be vigilant about having sufficient drugs on hand at trial sites before enrolling patients in a trial. “We’ve gotten calls from some of our sites asking for assistance with identifying suppliers [or] sharing drugs,” Dr. Buckner continued. “And our local pharmacies and institutions have been working cooperatively to ensure they have enough supplies on hand.”

Although lack of a drug in a study can slow or stop accrual to a clinical trial, Dr. Link said, the “looming problem” could be the analysis of data from trials in which many patients, because of a shortage, had to receive a drug that was not part of the original protocol. At this point, Dr. Mooney stressed, it’s very difficult to say how the shortage will affect the analysis of trials that had to rely heavily on alternative regimens.

Looking forward, said Dr. Link, several common themes and suggested fixes emerged from the November summit on the shortage. Although some will require legislation or regulatory changes, others are more straightforward: "We definitely need to improve communication between the FDA, the drug manufacturers, and the suppliers," he said.

As the global burden of cancer grows and the market for commonly used cancer drugs expands, Dr. McBride stressed, all of the stakeholders need to remain focused on this issue.

—*Carmen Phillips*