

Testimony submitted to the U.S. Senate Committee on Health, Education, Labor and Pensions

Full Committee Hearing on Prescription Drug Shortages:
Examining a Public Health Concern and Potential Solutions

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Good morning. My name is Dr. John Maris, Chief of the Division of Oncology at The Children's Hospital of Philadelphia and Director of our research institute's Center for Childhood Cancer Research. In addition, I am a Professor of Pediatrics at the University of Pennsylvania where I direct the Pediatric Oncology Program in our National Cancer Institute funded comprehensive cancer center.

I thank Chairman Tom Harkin and Senator Mike Enzi for holding this hearing today, in addition to Senator Bob Casey, Jr. who has made this and other issues impacting the lives of children a high priority.

The Children's Hospital of Philadelphia, or CHOP as it is more widely known, is the nation's largest pediatric healthcare network with over 50 locations throughout Pennsylvania and New Jersey. We have over 1 million patient encounters each year and are home to one of the largest pediatric research programs in the country. CHOP shares the highest ranking on U.S. News & World Report's Honor Roll of the nation's best children's hospitals. Our main hospital in West Philadelphia provides tertiary and quaternary care to a number of children having multiple chronic conditions or who are affected by rare pediatric diseases. Because of our high volume, we have an expansive need for generic drugs that are relatively common but we also utilize orphan drugs that are not widely used because of the high acuity and specialized nature of many of our patients.

As a physician focused on childhood cancer, my top priority is to make sure patients receive the best and safest care possible. As a researcher, I am dedicated to finding cures for cancer while minimizing or eliminating any side effects that result from the treatments we provide to this very vulnerable group of children. Both roles have enabled our research team to identify the main genes associated with neuroblastoma, an extremely aggressive form of childhood cancer. As a result, we have moved some of these discoveries toward new therapies, a number of which are now in clinical trials and we certainly hope will someday lead to a cure.

We work relentlessly to overcome obstacles in our work. The drug shortage we discuss today is one that has had a very potent impact on the progress we strive to make in research and clinical care. It slows down our progress and can even bring it to a grinding halt. Institutions like CHOP, and the National Institutes of Health, have invested significant resources towards translational research, where we convert our progress in the labs into treatments that may save lives in the hospital. However, without the drugs that are known to provide cures and form the backbone of our armamentarium, an important link in this chain is missing which can cause setbacks of epic proportions.

My goal in this testimony is to provide insight into our concerns at CHOP and share with you how we have responded to the drug shortages. I will close with some of my personal opinions on suggested solutions with the hope that they may help the committee in its efforts to address this pressing issue.

Beginning with our more broad concerns, I will tell you that there are a number of drugs we use commonly that are either in short supply or not available. These include life-saving cancer drugs used in my pediatric oncology patients, anesthetics used during surgery, and a large number of "sterile injectables" used by our neonatologists in many of our youngest and most vulnerable patients. In response to these shortages, CHOP's pharmacy developed a customized database that provides real-time information on our day-to-day supplies. The number of drugs in short supply at our hospital has been steadily increasing over the last few years to 123 drugs today, most of which are generic injectables. We are monitoring 35 drugs with a 4 to 8 week's supply; 9 drugs with a 2 to 4 week's supply; and, 10 drugs with less than 2 week's supply left. There are also 8 drugs that we have

completely run out of, forcing us to substitute potentially equally effective, but often less desirable, replacements.

This list includes:

- mitomycin injection, which is used for some surgical and ophthalmic procedures;
- co-trimoxazole (Bactrim) injection (which is available on a compassionate use basis), but a commonly used antibiotic to prevent serious infections in patients with compromised immune systems;
- diazepam (Valium) injection, which is used as a sedative in surgery and for seriously ill patients;
- pancuronium injection, which is used to immobilize patients for surgery;
- ammonium chloride injection which is used to alter the acid/base balance in critically ill patients; and
- Selenium, chromium and cysteine injections, which are all used to feed patients intravenously. The shortage of these agents poses a particularly dire situation for patients, often the neonatal population, who are unable to be fed in any other manner.

All of these shortages are presenting significant challenges to our medical staff and can have life-threatening consequences for our patients.

I would like to provide a recent example of how the drug shortage problem directly and seriously impacts children with cancer at CHOP, and how the consequences have a potentially dire impact in both the short- and long-term. For a six week period this past summer, CHOP was unable to obtain daunorubicin, a drug known to be essential for the cure of childhood leukemias—the most common pediatric malignancy—and part of our standard of care for over two decades. This drug is a big part of why we can offer curative approaches to the majority of patients. We were forced to use the drug doxorubicin as a replacement, despite there being no data available on the safety and effectiveness of this as a leukemia therapy or any other replacement. We did know, however, that withholding the drug altogether would definitely result in a much higher risk for relapse. While it is too soon to know if the substitution impacted the curability of these children, we noted significantly more side effects, mainly severe mouth and gut ulcerations, fever and infections. While no child died from these complications, it is my opinion that it is only a matter of time before this type of tragedy will occur. You must understand that delivery of cancer care to children requires a highly complex infrastructure. At any one time, we have about 50 children receiving chemotherapy at CHOP and there are over 300 different cancer treatment road maps written into our electronic health record. Absence of a single drug requires us to rewrite the formulary and roadmaps for each patient who may receive a substitution, a procedure that is highly complex, resource intensive, and frankly highly subject to human error. Finally, each of the children who received the substitution over the summer were in the midst of a clinical trial, and we are deeply concerned that these types of deviations from accepted practice will impact NCI-sponsored clinical trial results.

Another shortage we're experiencing here at CHOP includes some ingredients used in total parenteral nutrition (TPN), which is a way of supplying all the nutritional needs of the body by bypassing the digestive system and dripping a nutrient solution directly into a vein. The intravenous compound consists of carbohydrates, protein, fat, multivitamins, and numerous electrolytes and minerals essential to sustain life in patients unable to ingest food by other means. Approximately 50 percent of the patients admitted to CHOP's neonatal intensive care unit (NICU) have conditions such as gastrointestinal

abnormalities and/or extreme prematurity, which require TPN to survive. CHOP often finds that many of the ingredients essential to TPN are either completely unavailable or on shortage. For some of these ingredients, such as selenium (which is one of the injectables that we are completely out of), there is no substitution. For others, including sodium phosphate, there are alternative agents, but these alternative agents contain other ingredients (like aluminum) that may be harmful to patients, resulting in neurotoxicity or renal failure. The inability to provide appropriate TPN to patients may result in inappropriate nutrition, leading to electrolyte abnormalities, negative developmental outcomes (cognitive and physical), and longer hospitalizations. In order to prevent these complications, physicians, pharmacy and nutrition staff must invest a significant amount of time to develop an appropriate substitution, often limited to oral supplements. However, many children cannot take these due to their illness, leaving their families and doctors with no alternative. The only solution to this problem is the return of the electrolytes and trace elements in shortage, the major components of TPN, back to the market.

In most cases, we are able to address such challenges in our pharmacy. On a daily basis, our pharmacy purchasing staff monitors the availability of medications known to be in short supply nationally and enters this information into a customized database for tracking purposes. The Pharmacy has a weekly meeting of key personnel (supervisors, managers and clinical pharmacists) to review each shortage individually, update the status, and create a contingency plan for ongoing issues. Key physicians are contacted regarding shortages that may affect their patient population and plans for conservation and alternative therapies are created and implemented, often on an emergent basis, as there is often no notice that a medication is about to become unavailable. Conservation measures may require significant effort on the pharmacy department, in terms of re-distributing supplies, repackaging large quantities into smaller quantities, and tracking prescribers down to change orders. We have invested over \$2 million dollars by purchasing two "robots" which allow us to more efficiently use and repackage medications that we buy in large quantities. This allows us to stretch our supply and use every drop of a particular drug. The Hospital's response is designed to help us avert disruptions in patient care while ensuring the safety of our patients. These resources represent a significant financial investment, but help us mitigate the impact of drug shortages here at CHOP. All of these processes take a minimum of three full-time CHOP pharmacy staff persons.

While these efforts have helped us address these challenges, we have not overcome them entirely. I suggest this requires a partnership between providers, manufacturers and government. This begins by making sure that information on impending shortages is delivered responsibly and in real time. S. 296, legislation introduced by Senators Amy Klobuchar and Casey, coupled with President Barak Obama's executive order, will require drug makers to notify the Food and Drug Administration of shortages and this is an important step in the right direction. We need this information because the lack of notice of a medication becoming unavailable can put patients at significant risk, since many times there are not appropriate alternative therapies for some of these critically ill children, or those with rare diseases. Without notice, there is no time to conserve or prepare for a prolonged absence of a routinely used medication. Other critical information we need is an accurate estimate of re-supply dates. These are often a moving timeline that is continually being pushed into the future, without any target date in sight at all. Knowing when a medication will truly become available again would help us determine the most appropriate conservation practices. Abolishing "gray market" practices would also help assure patient safety, maximize legitimate supplies, and keep healthcare costs down.

For me, as someone who spends significant effort developing new therapies for cancer, the paradox is quite striking. The NCI infrastructure has supported major advancements in recent years in the

development of completely new and impactful treatments to cancer. However, each of these advances is built on the backbone of existing therapies, almost all of which are off patent at this time. It is quite striking that it is easier for me to get to my patients a drug discovered only recently and with a limited, and sometimes nonexistent, track record of curing children with cancer, but I cannot get them drugs that have been the bedrock of our curative therapies since the 1970's. Modern cancer therapy is not a replacement of the old ways; it is an integration and an enhancement of established curative methods. Without the bedrock of established and curative drugs, recent discoveries mean many of our most seminal advances in the field are in jeopardy of being reversed due to this issue.

I close today by commending this committee for not only investigating the issue, but for also helping to identify a solution for it. While I have shared insight into how The Children's Hospital of Philadelphia is addressing drug shortages, I will tell you that our efforts have required us to be nimble and shift resources away from other priority child health demands, so that we may address this important problem. We have very high standards for patient care and safety and we will not allow this crisis to compromise that. As a pediatric oncologist, I am awestruck at how such an issue can so dramatically impact the children afflicted with cancer and the research infrastructure we have built over decades to arrive at curative therapy for all. As standards continue to rise, as they should, the tools that help doctors provide excellent patient care need to be readily available and continuously improved. These tools include pharmaceuticals. We must remember at the epicenter of this issue is the patient and I hope the information I shared will further invigorate your efforts to ensure that drugs are readily available for the people that depend upon them most.