

## Persistent drug shortages jeopardise patient safety in the USA

Drug shortages affect clinical care “on a daily basis” across the USA, according to the Society of Critical Care Medicine’s president Craig Coopersmith (Emory School of Medicine, Atlanta, GA, USA) and other experts interviewed by *The Lancet Respiratory Medicine*. Ongoing shortages are costly for hospitals and jeopardise patient safety, they note.

The US Food and Drug Administration (FDA)’s authority to address shortages was expanded in 2012. The agency has 25 full-time employees working on shortages—up from three workers in 2011—and now requires manufacturers to report impending disruptions. Although this move seems to have helped to curb the number of new drug shortages, existing shortages persist.

“That’s one of the most frustrating things”, says Erin Fox (Drug Information Service, University of Utah, Salt Lake City, UT, USA). “It’s very good that the new shortages are decreasing. But we’re not seeing enough movement by manufacturers to address existing shortages.”

Ongoing drug shortages grew from 150 in 2010 to nearly 300 in late 2012, Fox reports. “Unfortunately, we’ve seen it stay at that number through 2014.”

Generic sterile injectable drugs have been hardest hit, says Bona Benjamin (American Society of Health-System Pharmacists [ASHP], Washington, DC, USA). Shortages have affected opioids, heparin, antibiotics, and even saline fluids and injectable electrolytes, dextrose, lipids, and aminoacids. Supplies of cardiology critical care drugs such as nitroglycerin, dopamine, and calcium injections have also been disrupted. The ASHP and Society of Critical Care Medicine’s Drug Shortages Task Force track and offer educational materials and guidance on the management of drug shortages.

“It’s a huge problem for our hospital”, says Shannon Carson (University of

North Carolina’s School of Medicine, Chapel Hill, NC, USA). “Shortages are so common and so frequent that we’ve had to reassign a full-time pharmacy employee just to deal with various suppliers to make sure we stay ahead of upcoming shortages and get suitable replacements in place.”

Sedative shortages are “a big problem”, Carson says. “We know we should use short-acting sedatives to lessen time on the ventilator, but when they’re in short supply, we have to revert back to benzodiazepines, which are associated with worse outcomes.”

When 250 mL bags of saline fluid are unavailable, pharmacists revert to 100 mL bags, and must recalculate concentrations of infused drugs and reprogramme pumps, Carson notes.

Shortages of antibiotics have affected clinicians’ ability to manage drug-resistant and other infections.

“We were no longer able to obtain premixed, patient-controlled analgesic syringes”, Carson adds. “The hospital had to switch to new pumps and that was no small matter; we have thousands of pumps and they’re programmable and store dosage libraries. You have to change everything in your formulary, retrain hundreds of nurses on how to use the pumps. They’re technical devices; when everybody is new to the pump, errors are going to happen, and did happen—making this a major safety issue as well as a major expense.”

Shortages have also spurred activity by the so-called grey market and increase the risk that counterfeit or adulterated drugs will enter the supply chain. “Many centres have a blanket prohibition on grey market distributors”, Fox notes. “In some states, they are also illegal.”

Even if such distributors can offer a valid pedigree for the drug, “you don’t know if the drug’s been stored properly or tampered with”, cautions Benjamin. “It can be a difficult dilemma when you

have a really sick patient and there’s only one way to get the drug. But pharmacists know it’s a real caveat-emptor situation.”

The roots of the problem are complex. “There are a lot of conspiracy theories”, but little evidence for intentional or artificial shortages, Coopersmith says. Contributing factors can include aging facilities, production capacity issues, shortages of raw materials, regulatory barriers, and spikes in demand.

“Very technical” manufacturing issues can also arise, a survey by the International Society of Pharmaceutical Engineers (ISPE) showed. “Certain sterile injectable products are delivered in powder form, and making them is a complex process”, explains Joseph Famulare (ISPE, Washington, DC, USA).

Because there are few US manufacturers of generic drugs, a problem at one facility can trigger nationwide or even global shortages. When one facility encounters a manufacturing problem, “it’s not easy for a miraculous ramp-up at other facilities” to meet demand, Famulare notes. ISPE is helping train its members how to conduct gap analyses and address problems.

“There’s virtually no resiliency in our drug supply chain”, Fox says. “The majority of shortages are caused by

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For more on the FDA’s efforts to address drug shortages see <http://www.fda.gov/Drugs/Drugsafety/DrugShortages/default.htm>

For Erin Fox and colleagues’ report on the complex health-care crisis posed by drug shortages see *Mayo Clin Proc* 2014; **89**: 361–73

For ASHP’s drug shortages database and guidance see <http://www.ashp.org/menu/DrugShortages>

For more on Society of Critical Care Medicine’s Drug Shortages Task Force see <http://www.sccm.org/Research/Pages/Current-Issues.aspx>

For the ISPE’s survey of drug makers see <http://www.ispe.org/drugshortages/2013JuneReport>

For more on the ISPE’s efforts to help manufacturers prevent drug shortages see <http://www.ispe.org/drugshortages>



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manufacturing problems. A glitch often means a facility has to close down because they don't have extra capacity if there's a problem. The generic manufacturing lines typically make many products on the same line, so a problem on one line can affect 20 products."

It is unclear how many patients have been harmed or died as a result.

"There's no system for tracking it", Coopersmith notes. "It's almost impossible, because frankly, shortages are always changing and varying....It's important that there be more formal studies on patient safety. Every one of us believes there are important issues for patient safety but there have been no broad-based studies of just how impactful it is."

Supplying code carts has been a "constant problem", Carson is quick to note: epinephrine injection systems were in short supply, so code carts are stocked instead with multidose vials that must be measured during life-saving efforts.

"In the urgency and confusion of a code, you can imagine the potential for drug errors."

The costs to hospitals of drug shortages have been substantial, but are difficult to quantify precisely, experts say. Personnel costs are mounting, notes Carson. "The ordering and reordering and investigating what suppliers have, is a constant job for one of our senior pharmacists. Pharmacists have to constantly attend meetings to come up with creative workarounds to deal with the next shortage, or multiple shortages that occur simultaneously."

There are no easy solutions. "If it were simple, it would've been fixed already", says Carson.

The FDA can speed up approvals and inspections, encourage increased production, or extend expiration dates. "But they cannot require somebody to increase production or even continue production, or to disclose why there's a shortage", Coopersmith notes.

The FDA advocates improved transparency through the use of quality matrices for manufacturers, with which hospitals might make purchasing decisions that help to reduce the risk of supply disruptions.

"ISPE is leading a data-driven approach, signing up 18 companies" for a pilot study to identify what metrics best predict the reliability of a manufacturing facility, Famulare says. A final report of the pilot project should be released in June, 2015.

The FDA can allow importation of drugs produced abroad but that's a stop-gap, says Benjamin: "Importation is never a magic bullet because the US uses a tremendous number of drugs—think about the dialysis patient population alone; it gives manufacturers a chance to work harder to ramp up production."

Industry, not hospitals and regulators, must ultimately find solutions, Benjamin says. "The ball is in their court now."

*Bryant Furlow*