USP <800> Adds Significant Safety Standards

Facility Upgrades Needed to Protect Employees From Hazardous Drugs

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USP <800>, the U.S. Pharmacopeial Convention’s new standard for handling hazardous drugs (HDs) in health care settings,1 is requiring millions of dollars in capital outlays for facility and equipment upgrades in hospital-based pharmacies and elsewhere nationwide. The standard, which becomes effective on July 1, 2018, also requires in-depth assessments of each HD that facilities handle, significant workflow and work practice changes, and thorough staff training.1

The newest USP standard builds upon 2008’s USP <797>, which focused primarily on minimizing the risk of contaminating medicines when compounding sterile preparations.2 In contrast, USP <800> is aimed primarily at protecting all health care workers, as well as patients and the general public, who have access to any facilities where HDs are prepared. These workers include pharmacists, technicians, nurses, physicians, physician assistants, home health care workers, veterinarians, and veterinary technicians.

The new chapter addresses the entire life cycle of an HD, from the time it is delivered to a facility through its storage, preparation, and administration, as well as the handling and disposal of any hazardous waste that these processes produce. Specifically, the 18-page chapter delineates requirements that cover the responsibilities of personnel handling HDs; facility and engineering controls; procedures for deactivating, decontaminating, and cleaning; spill control; and documentation.

Affected entities include all those that store, transport, prepare, or administer HDs—including pharmacies, hospitals, and other health care institutions, patient treatment clinics, physicians’ practice facilities, or veterinary offices.

“The intent and scope of USP <800> is much broader than some of the requirements found in USP <797>,” says Patricia C. Kienle, RPh, MPA, FASHP, who served on the USP 2015–2020 Compounding Expert Committee that wrote the chapter. “It starts with the guy on the loading dock who first receives the drugs, all the way through to the nurses who administer them. While it focuses on the protection of health care workers, it’s also about patient safety. By keeping ourselves safe, we are protecting our patients as well.”

Corbin Bennett, PharmD, MPH, Senior Director of Oncology and Outpatient Infusion Pharmacy Services with Kaiser Permanente’s National Pharmacy Programs and Services, views the USP <800> standards as a much-needed single-source guide for handling HDs.

“Despite the challenges it represents,” he says, “I think USP <800> is a great document that is giving our organization and me, as a pharmaceutical leader, more direction on how to set policy and identify what needs to be done for employee safety while handling hazardous drugs. Previously, you had to pull together quite a few different sources and references—including OSHA [the Occupational Safety and Health Administration], NIOSH [the National Institute for Occupational Safety and Health], ASHP [the American Society of Health-System Pharmacists], and ONS [the Oncology Nursing Society]—to develop a recommendation, so having this one source of truth is quite a benefit.”

According to USP, growing evidence accumulated over the course of decades indicates that acute and chronic health effects can occur due to occupational exposure to more than 200 HDs commonly used in health care settings. Since 1994, more than 100 studies have documented evidence of contamination of the work environment with HDs, according to a joint 2015 statement by ONS, the American Society of Clinical Oncology, and the Hematology/Oncology Pharmacy Association.3

In addition, the joint statement noted, more than 50 studies have demonstrated the presence of HDs in the urine of health care workers, indicating actual exposure. The statement added that, according to the Centers for Disease Control and Prevention (CDC), occupational exposure to HDs has been associated with acute symptoms such as nasal sores and hair loss, adverse reproductive outcomes such as infertility and miscarriages, genetic changes such as DNA damage, and an increased occurrence of cancer.3

“The CDC says about eight million health care workers are exposed to these drugs each year,” says Rick Schnatz, PharmD, Senior Manager of USP’s Healthcare Quality and Safety Group. “We want to prevent either acute or long-term effects of these drugs.”

The USP <800> chapter, which was published in its final form on February 1, 2016, was developed by the USP Compounding Expert Committee with the assistance of the USP Compounding with Hazardous Drugs Expert Panel and government liaisons from the Food and Drug Administration (FDA) and the CDC, including NIOSH.

Although USP is a scientific nonprofit organization, its standards—such as USP <800>—are enforced by a variety of local, state, and federal regulatory agencies and are also followed worldwide. Accrediting bodies such as The Joint Commission survey for compliance with USP compounding standards. The Centers for Medicare and Medicaid Services State Operations Manual refers to USP standards.

An increasing number of state pharmacy boards have also adopted USP standards. A Pew Charitable Trusts report recently indicated that of the 43 states that had responded to its survey questions, 21 (49%) indicated they required sterile compounding that fully conforms to USP <797> standards; another 13 (30%) reported mandating at least some portions of that USP chapter.1 Among those that require full compliance are California, which on January 1, 2017, became the first state to also adopt the new USP <800> standards.

The unusually long, nearly two-and-a-half-year lag between the time the final standards were published on February 1, 2016, and their effective date on July 1, 2018, was designed, Dr. Schnatz says, to allow pharmacies and other health care facilities to undertake any necessary engineering controls and plan for the costs associated with facility and equipment upgrades.
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facilities time to obtain budget approvals and modify their facilities and procedures.

“I don’t mean to minimize the impact in terms of facility changes and capital dollars required, but the first public version of USP <800> was released in March 2014, so pharmacies have really had four years to prepare for it,” adds Kienle, Director of Accreditation and Medication Safety with Cardinal Health Innovative Delivery Solutions, a health care consulting firm based in Dublin, Ohio. “It’s not a surprise.”

**Required Upgrades**

With several exceptions, Kienle and Dr. Schnatz both note that pharmacies with facilities that complied with USP <797> generally will be compliant with USP <800> standards. The revisions include the following requirements:

- Compounding of HDs must be performed:
  - In containment primary engineering control (C-PEC) devices with external ventilation situated in walled-off rooms that function as containment secondary engineering controls.
  - Under negative pressure that ranges from 0.01 to 0.03 inches of water column (inch WC) relative to all adjacent areas.
  - With at least 12 air changes per hour.
  - With venting directly to the outside.

- HD storage areas, including rooms in which HDs are stored in refrigerators, are subject to the same negative air pressure requirements as compounding areas.

- HDs must be stored and prepared in areas separate from areas where non-HDs are similarly handled, and unless certain conditions are met, the compounding of sterile and nonsterile HDs must be done in separate rooms. An exemption permitted under USP <797> that allowed small volumes of HDs to be compounded in the same areas as non-HDs has been eliminated.

- Personal protective equipment (PPE)—gowns; head, hair, and shoe covers; and two pairs of chemotherapy gloves—is required for compounding both sterile and nonsterile HDs, and two pairs of such gloves are required for administering antineoplastic HDs. Facilities also need to develop standard operating procedures regarding appropriate PPE for any workers who otherwise handle HDs.

- Closed-system transfer devices (CSTDs) are mandated to minimize the exposure to nurses who administer HDs.

Explaining the elimination of the exemption that allowed small volumes of HDs to be compounded in the same areas where non-HDs are prepared, Dr. Schnatz says: “Any risk is too much of a risk.”

“If your pharmacy has been using the low-volume exemption with a chemotherapy compounding hood in a positive-pressure room where nonhazardous IV [intravenous] drugs are also prepared, that’s not safe,” Kienle adds. “That compounding will now have to occur under negative pressure.”

Standards previously allowed some HD compounding hoods to be vented into an adjacent room if the air in that room was then vented outside. However, USP <800> requires that all such compounding be vented directly outside.

In addition, USP <797> required negative air pressure of at least 0.01 inch WC for such venting, but USP <800> dictates an acceptable range of only between 0.01 and 0.03 inch WC. “If you have too much suction you will pull air in through unfiltered areas—through cracks and crevices, sprinkler heads, and conduits running through the rooms—and you will suck contamination into the room and risk contaminating the drugs people are taking,” explains Jim Wagner, a member of the USP Compounding Expert Committee and President of Controlled Environment Consulting in Hellertown, Pennsylvania.

For the compounding of sterile HDs, the most hazardous drugs will require ISO Class 7 buffer rooms and ante-rooms. However, another new wrinkle of USP <800> permits the compounding of low- and medium-risk HDs in C-PEC compounding hoods that are situated in rooms called containment-segregated compounding areas, which do not require classification. This design offers a less expensive way for organizations to comply, provided they can work with the short beyond-use time allowed in this design.

As for requiring CSTDs, Kienle says, “In the pharmacies we have all these protection hoods, garb, and room venting, but then the drugs have been handed off to nurses who have had none of that protection. CSTDs contain the hazardous drugs so that they don’t become toxic to the nurses while they are administering them to patients.”

Dr. Schnatz adds: “CSTDs keep any drug vapors from affecting nurses or having the drugs aerosolize in a room where other patients and support personnel could be exposed.”

Nishaminy Kasbekar, PharmD, FASHP, Corporate Director of Pharmacy for the University of Pennsylvania Health System (Penn), and her staff are testing CSTD products to ascertain whether they meet USP <800> standards. “Some vendors claim their CSTD products are closed systems, but some of them truly are not,” she said. Indeed, in September 2015, NIOSH noted that of five CSTDs it had tested, only two prevented the escape of drug vapors.

**Cost of Facility Upgrades**

According to several major health care systems, the cost of redesigning their pharmacy facilities to meet the new standards could exceed $1 million for each compounding area depending on the location and other factors.

Penn recently spent up to $1.5 million on each of three USP <800>-compliant clean rooms. “The costs are primarily in the environmental controls, such as the HVAC [heating, ventilation, and air conditioning] systems, as well as in facility design,” Dr. Kasbekar says.

Penn operates five hospitals in the Philadelphia area and multiple clinics, including ambulatory cancer centers, in Pennsylvania and southern New Jersey. One problem: limited space within buildings. In the past, given the system’s tight building configurations, it was difficult to meet venting requirements for the compounding areas. “But now USP <800> is saying that you have to maintain negative pressure not just where we compound the drugs but where we store them,” she says. “That’s our biggest issue.”

The requirement that the negative pressure must range between just 0.01 and 0.03 inch WC is another significant cost driver, according to Kaiser Permanente’s Dr. Bennett.
“Originally, we thought this would be rather straightforward because we’ve been building our pharmacies, including those we opened just two to three years ago, with negative pressures that exceed 0.01,” he says. “But some of those negative pressures are 0.05 to 0.07, and we’re finding that ratcheting those negative pressures underneath the 0.03 cap requires very precise, sophisticated HVAC design.”

With this year’s acquisition of Group Health, based in Washington State, Kaiser Permanente now has nearly 150 hospital- or clinic-based sterile compounding pharmacies from coast to coast that prepare both HDs and non-HDs. Every pharmacy has required at least some modifications dictated by USP <800>. Dr. Bennett—who about 20 months ago estimated that it would cost between $1.5 million and $2.5 million to redo each compounding pharmacy—now says, “It could be more.”

In response to the financial and facility requirements, instead of building and maintaining three or four sterile compounding units on its large hospital campuses, Kaiser Permanente is considering consolidating and reducing the number of such pharmacies. Otherwise, Dr. Bennett says, “We will either be compliant by July 1, 2018, or we will not be compounding hazardous drugs in those particular pharmacies.”

Another factor health care organizations need to consider, Penn’s Dr. Kasbekar adds, is the increased operational costs generated by required maintenance and monitoring.

In particular, all of these factors could impact smaller health care organizations with compounding pharmacies, including rural critical-access hospitals with 25 or fewer acute care inpatient beds. “I wonder,” Dr. Kasbekar says, “if some smaller hospitals will just start outsourcing these drugs because of increased financial demands or space constraints.”

Dr. Bennett notes that mobile units could be another option.

First Step: A Drug-by-Drug Assessment

In addition to facilities and equipment changes, one of the keys to assuring compliance with USP <800> is for pharmacies to conduct an in-depth assessment of all the HDs they deliver to patients. That assessment begins with reviewing the NIOSH alert that lists the HDs found in health care settings. The NIOSH list encompasses three groups of drugs:

- **Group 1:** Antineoplastic (anticancer) drugs that may also pose a reproductive risk for susceptible populations.
- **Group 2:** Nonantineoplastic drugs that meet one or more NIOSH criteria for an HD. Some of these may also pose a reproductive risk for susceptible populations.
- **Group 3:** Drugs that primarily pose a reproductive risk to men and women who are actively trying to conceive and women who are pregnant or breast feeding.

The NIOSH list of HDs found in health care settings was first published in 2004 and subsequently updated four times. The last biennial update occurred in 2016.

In addition to reviewing the NIOSH-listed drugs that a facility handles, Dr. Bennett recommends also identifying any additional HDs a facility might administer that have been approved by the FDA since the compilation of the most recent NIOSH list, which was published for public comment in 2015.

According to Kienle, any antineoplastic drug (except those in solid oral dosage forms that require only counting or packaging) listed in NIOSH’s group 1 requires full compliance with the USP standards. But organizations may be able to develop less stringent, alternative strategies for adequately protecting their health care workers when they handle group 2 and group 3 drugs, which include antibiotics, diuretics, and anti-psychotics. The key, she says, is how the drugs are formulated, and whether or not pharmacies have to manipulate them in any way before they are administered to patients. Such manipulation can include crushing or splitting tablets or opening capsules; pouring oral or topical liquids from one container to another; weighing or mixing components; constituting or reconstituting powdered or lyophilized HDs; and/or withdrawing or diluting injectable HDs from parenteral containers.

Any such manipulations will require pharmacies to develop containment strategies to protect health care workers. However, Kienle notes, “It’s very likely that, for the vast majority of the drugs in groups 2 and 3, pharmacies may not need to do anything different than how they are handling them now other than identifying them on their list of hazardous drugs and letting their staff know that they are hazardous drugs. For example, most pharmacies probably buy spironolactone, a diuretic listed in group 2, in a unit-dose package from the manufacturer and do not manipulate it.”

However, if facilities handle and administer different formulations of a single drug, USP <800> requires them to develop risk-containment strategies for each formulation.

### RESOURCES

**U.S. Pharmacopeial Convention**
- The *USP Compounding Compendium 2017*, which includes USP <800>, is available by subscription or for purchase at: [www.usp.org](http://www.usp.org).
- A USP <800> updates newsletter is available by request at: [www.usp.org/HQS-Signup-Form](http://www.usp.org/HQS-Signup-Form).
- USP is offering one-day classroom training (in Bethesda, Maryland) or live webcast training on USP <800> on June 14, 2017. The course has been approved by the National Association of Boards of Pharmacy (NABP) and the NABP Foundation for 6.5 continuing pharmacy education credits for pharmacists and pharmacy technicians. Information is available at: [www.usp.org/meetings-courses/calendar/2017-06](http://www.usp.org/meetings-courses/calendar/2017-06) (Click on Course Session on June 14).

**American Society of Health-System Pharmacists**
- *The Chapter <800> Answer Book*, by Patricia C. Kienle, will be available in May via [www.ashp.org](http://www.ashp.org).

**The Joint Commission**
- A free Web-based hazardous drug tool kit to assess an organization’s readiness for the implementation of USP <800> is available at: [https://hazmedsafety.com](https://hazmedsafety.com).

**National Institute of Occupational Safety and Health**
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“You may have a drug that comes in different formulations, from an oral tablet to a liquid in either a syringe or an IV bag,” Dr. Bennett says. “If it’s an oral tablet packaged in a unit-dose plastic bubble pack, you obviously are going to handle it differently than if it’s an open syringe of liquid HD. That’s a big challenge for our working group.”

Training Must Be Documented

USP’s Dr. Schnatz recommends that any training of health care personnel who could be exposed to HDs should cover the entire 18-page USP <800> chapter—“whether or not they touch these drugs every day.” The standard requires facilities to train all personnel who handle HDs and to assess their resulting competencies—both of which must be documented. Personnel competency reassessments are required at least once a year, as well as training prior to the introduction of new HDs or equipment or before new or significant changes in processes or safe operating procedures.

One of the challenges, Dr. Bennett says, will be training much more of a hospital’s nursing staff regarding the importance of what PPE to wear and when to wear it.

“This is ‘old hat’ for nurses and pharmacists who work in an oncology setting,” Dr. Bennett says. “They’ve been wearing personal protection equipment for a long time. But with the list of HDs covered by USP <800> expanding beyond just chemotherapy drugs, you have a lot more nurses working, for instance, on medical–surgery floors, who need to be trained on the definition of an HD and the need to wear PPE.”

“Part of the message will involve noting that some of the listed drugs are ones that nurses have been administering for 30 years with just standard precautions. They are now deemed hazardous and need to be treated differently,” he adds.

Additional Recommendations

USP <800> also recommends, but does not require, certain procedures, including ongoing medical surveillance plans and environmental wipe samples.

Ongoing medical surveillance plans would encompass identifying all employees with potential exposure to HDs; developing initial baseline assessments of each worker’s health status and medical history; and assessing and documenting any symptom complaints and lab tests, such as blood counts, to gauge potential health impacts. Such assessments, USP contends, can also be viewed as a secondary prevention tool that can detect any exposure-related health problems early.

“It’s a good idea, but it’s not something that the pharmacy or nursing departments should do alone,” Kienle says. “It should be a system-wide policy and practice developed by the human resources and risk management departments.”

At least every six months, USP <800> also recommends that health care facilities collect environmental wipe samples to determine if any HD residues can be found on the surfaces of equipment, adjacent rooms, pass-through chambers, and patient administration areas. As USP notes, there is no standard for acceptable limits for HD surface contamination.

If the wiping samples detect residues of HDs commonly assayed with wipes, such as cyclophosphamide, ifosfamide, methotrexate, fluorouracil, or platinum-containing drugs, the facility’s designated HD person should make sure the areas are cleaned and decontaminated and devise ways to minimize the chances of the HD residues reoccurring.

REFERENCES