The Future Impact of USP 800 in the Health Care Setting

By Ashley Tocco, Pharm.D., BCPS, lead IV room pharmacist, Bronson Methodist Hospital

Target Audience
This continuing education activity was developed specifically for pharmacists and pharmacy technicians.

Disclosure Statement
The author has indicated that she does not have any conflicts of interest, nor does she have financial relationships with a commercial interest, related to this activity.

Learning Objectives
At the end of this activity, participants should be able to:
• state the definition of a hazardous drug
• identify drugs which are hazardous in nature
• identify potential health risks associated with exposure to hazardous drugs
• recognize differences between required engineering controls for nonsterile and sterile hazardous drug compounding
• explain how to create a medical surveillance program within a health system

Each year, approximately 8 million U.S. health care workers are potentially exposed to hazardous drugs (HDs). Over the years, exposure to hazardous agents in the workplace has become a concerning topic for health care workers, as more and more studies show an increased risk of various health problems associated with exposure. One health risk identified in health care workers that has been associated with exposure to antineoplastic agents is compromised reproductive health and fertility, including increased risk for spontaneous abortion. A study published by the American Journal of Obstetrics and Gynecology found that nurses who were exposed to antineoplastic agents had a two-fold increased risk of spontaneous abortion. This risk has been demonstrated most prominently in the female nursing population, but some studies have demonstrated risk associated with exposure in pharmacists and pharmacy technicians as well. One study examining 7,094 pregnancies of 2,976 nursing and pharmacy staff found an increased risk of spontaneous abortion among exposed employees and an increased risk of combined spontaneous abortion and stillbirth but not an increased risk of stillbirth alone. A meta-analysis of 14 studies published in 2005 found no increased risk associated with congenital malformations or stillbirths, but did find an increased risk of spontaneous abortion in female healthcare workers exposed to cytotoxic agents.

Aside from reproductive consequences, there is a small body of literature demonstrating an increased risk for cancer in those with occupational exposure to antineoplastic agents. The Centers for Disease Control and Prevention (CDC) recognize that the literature regarding cancer risk as it relates to exposure to antineoplastic agents is limited and is composed mainly of case reports and epidemiological studies. However, it should be recognized that a risk may exist and proper studies may not have yet been published. Along with antineoplastic drugs, nonantineoplastic hazardous agents such as anti-viral drugs, hormonal agents and bioengineered drugs have also been associated with adverse effects in exposed employees such as skin rashes, reproductive problems and possibly leukemia and other cancers.

• In 2004, the National Institute for Occupational Safety and Health (NIOSH) published a safety alert, which included a listing of agents that should be considered hazardous and should be handled according to specific recommendations. The list was most recently updated in 2014 to include 27 additional drugs. According to NIOSH, a hazardous drug
is one that exhibits one or more of the following six characteristics in humans or animals:

- Carcinogenicity
- Teratogenicity or other developmental toxicity
- Reproductive toxicity
- Organ toxicity at low doses
- Genotoxicity
- Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria

The U.S. Pharmacopeial Convention (USP) is a nonprofit organization that sets standards for various activities and areas of health care, which are enforceable by the Food and Drug Administration (FDA). Recently, the USP proposed a new chapter to their publication “The United States Pharmacopeia and the National Formulary” (USP-NF) entitled “USP General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings” or simply USP <800>. USP-NF General Chapters numbered below <1000> provide required guidelines and these chapters can be used by the FDA and other bodies to evaluate health system compliance. Therefore, once published, health systems will be expected to be in compliance with recommendations outlined in USP <800>. Health care organizations should, therefore, begin thinking about necessary changes that will need to be made in their facilities in order for compliance to be met.

In general, USP <800> builds on the standards and recommendations set forth by both “USP <795> Pharmaceutical Compounding – Nonsterile Preparations” and “USP <797> Pharmaceutical Compounding – Sterile Preparations,” with an emphasis on protecting personnel by containment of hazardous drug exposure to as low a level as reasonably achievable. The chapter covers handling of hazardous drugs through various phases of the handling process, including but not limited to receiving and unpacking, preparing, compounding, dispensing and administering. A designated compounding supervisor should be assigned within the organization who will be responsible for ensuring compliance is met with respect to all areas of the chapter, environmental controls are appropriate and in good working condition, and personnel are adequately trained in handling of hazardous drugs.

**Storage of Hazardous Drugs**

As a general rule, hazardous drugs should be stored in such a way that they are separate from nonhazardous drug inventory. An exception is made for those hazardous drugs that are present in their final unit dose or unit-of-use packaging; these products may be placed among all other pharmacy inventory as long as they are labeled as hazardous in nature with requirements for proper handing made apparent. Hazardous drugs that are separated from other drug inventory should be stored in a room with negative pressure relative to adjacent spaces with at least 12 air changes per hour. Hazardous drugs that require refrigeration should be stored in a dedicated refrigerator separate from non-hazardous drugs. Sterile and nonsterile drug inventory may be stored together. However, storage within a sterile compounding area is to be limited to sterile hazardous drugs only.

**Engineering Controls**

USP <800> outlines three types of containment engineering controls that should be present when compounding hazardous drugs: primary, secondary and supplemental. For the sake of simplicity, a containment primary engineering control (C-PEC) is the hood or work surface in which hazardous drugs are being prepared, a containment secondary engineering control (C-SEC) is the room in which the hazardous drugs are being prepared and the supplemental engineering control refers to items such as closed-system drug-transfer devices (CSTDs).
As a general rule, regardless of the type of compounding, the C-PEC is required to be externally vented. Therefore, a laminar airflow workbench (LAFW) or compounding aseptic isolator (CAI) shall not be used to compound hazardous drugs. In addition, the C-SEC should be a segregated room dedicated to hazardous drug compounding, which should be maintained at negative pressure relative to adjacent spaces and have the appropriate number of air exchanges based on the type of compounding taking place. Hazardous drugs should never be manipulated in an area that is of positive pressure in relation to adjacent spaces, as this would allow for contamination of adjacent spaces by outward airflow.

Closed-system drug-transfer devices should be considered highly recommended during compounding of hazardous drugs by pharmacy staff and should be considered required during administration of hazardous drugs by nursing personnel when the dosage form allows. It is recognized that some dosage forms such as intrathecalcs, irrigations, ophthalmic preparations and topical agents may not allow for a CSTD to be used. Wick and colleagues published a study evaluating employee exposure prior to and after implementing a CSTD. They found that prior to CSTD use, six out of eight employees (nurses, pharmacists, pharmacy technicians and a control) were found to have cyclophosphamide present in their urine and two out of those eight were found to have ifosfamide present in their urine. After implementation of a CSTD, the urine of all eight employees was found to be free of both agents. Various closed-system drug transfer devices have been approved by the FDA and pharmacies should take care to evaluate each device for appropriateness within their organization.

Nonsterile HD Compounding

A Containment Ventilated Enclosure (CVE), commonly referred to as a powder hood, or a Class I Biological Safety Cabinet (BSC), should be used for preparation of nonsterile HD compounds. However, a Class II BSC or a Compounding Aseptic Containment Isolator (CACI) may be used for nonsterile HD compounding if it is dedicated to nonsterile HD compounding. The hood in which nonsterile HD compounding takes place does not need to be contained in an ISO Class 7 room as the compounding is nonsterile in nature. However, the room still needs to meet requirements of a C-SEC such as segregation from other areas and maintenance at negative pressure (see Table 1).

Sterile HD Compounding

According to USP <800>, sterile HD compounding must take place in a Class II BSC or a CACI. The chapter allows for the hood to be placed in an ISO Class 7 environment, which is the most sterile means of compounding. However, USP recognizes that an ISO Class 7 environment may not always be available, especially in oncology clinics where compounding is taking place or smaller institutions without dedicated cleanrooms. The chapter, therefore, allows for HD compounding alternatively to take place in a containment segregated compounding area (C-SCA) that does not contain ISO Class 7 air with the expectation that one of the following conditions is met (see Table 1):

- A CACI is present (USP 797 beyond use dating may be applied in this situation).
- A BSC is present, all compounding meets low- or medium-risk compounding definitions, and finished products are given a maximum beyond use date (BUD) of 12 hours.

Regardless of the lack of ISO Class 7 air, the C-SCA still needs to meet all requirements for a C-SEC (i.e., segregated room, negative pressure, appropriate air exchanges, etc.). This differs from a previous recommendation published in USP <797> allowing facilities that compound a small volume of hazardous drugs to have a BSC or CACI for hazardous drug compounding in a non-
negative pressure room.

A Class II BSC or CACI that is mainly used to prepare sterile products may be used for occasional nonsterile drug preparation with the expectation that the device will be thoroughly cleaned and disinfected prior to resuming sterile compounding operations. However, if a large volume of nonsterile HD compounding is expected to take place, a dedicated nonsterile HD compounding hood should be present and contained in a segregated room from the hood used for sterile HD compounding unless the hood used for nonsterile HD compounding is effective enough that the room can continuously maintain ISO Class 7 air throughout nonsterile HD compounding operations.

Table 1. Acceptable Configurations for Hazardous Drug Compounding

<table>
<thead>
<tr>
<th>Compounding Function</th>
<th>C-PEC</th>
<th>C-SEC</th>
<th>Air Changes Per Hour (ACPH)</th>
<th>Maximum BUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsterile Compounding</td>
<td>CVE Class I BSC</td>
<td>Any C-SEC</td>
<td>12 ACPH (exhaust)</td>
<td>As listed in &lt;795&gt;</td>
</tr>
<tr>
<td>Compounding Sterile HD in a Cleanroom</td>
<td>Class II BSC CACI</td>
<td>ISO 7 Classified</td>
<td>30 ACPH (HEPA supply)</td>
<td>As listed in &lt;797&gt;</td>
</tr>
<tr>
<td>Compounding Sterile HD in a CACI Not in a Cleanroom</td>
<td>CACI</td>
<td>C-SCA</td>
<td>12 ACPH (exhaust)</td>
<td>As listed in &lt;797&gt;</td>
</tr>
<tr>
<td>Compounding Low- or Medium-Risk Sterile HDs in a BSC Not in a Cleanroom</td>
<td>BSC</td>
<td>C-SCA</td>
<td>12 ACPH (exhaust)</td>
<td>12 hours</td>
</tr>
</tbody>
</table>

i. Adapted from Table 3 and Table 4 of Proposed USP General Chapter <800>

Nonhazardous Drug Compounding

On occasion, some institutions utilize the C-PEC dedicated to hazardous drug compounding for preparation of nonhazardous agents. USP <800> allows the practice of compounding nonhazardous drugs to continue to take place on occasion in a hood dedicated to hazardous drug compounding with the expectation that the final compounded product is placed in a protective outer wrapper prior to removal from the hood and is labeled to require personal protective equipment (PPE) handling precautions.

STOP AND REFLECT

You are the compounding supervisor within your organization. You receive a phone call from an oncology clinic that is in your health system stating that they have a CACI but it is not currently contained in an ISO Class 7 cleanroom. They would like to know if their current hazardous drug compounding configuration is compliant with the new USP <800> recommendations. What requirements would their C-SEC need to meet in order for the oncology clinic to maintain compliance with USP <800>?

Personal Protective Equipment

USP <800> requires that PPE be worn by all personnel involved in any step of the hazardous drug handling process. Wearing PPE should not be limited to those personnel who are directly involved in compounding, preparing or administering hazardous drugs such as pharmacists,
pharmacy technicians and nurses. In fact, the *American Journal of Health-System Pharmacists* published an article in 2005 that evaluated three studies looking at vial contamination of chemotherapeutic agents. All three studies found surface contamination of vials of cyclophosphamide, ifosfamide, fluorouracil and cisplatin obtained from commercial manufacturers in both the United States and Europe. These studies stress the importance of proper handling through the entire hazardous drug process. It is expected that, in addition to those employees preparing and administering hazardous drugs, PPE will also be worn by employees that are involved in receiving, transporting and stocking hazardous drugs such as the pharmacy buyer and transportation staff as well as those employees involved in disposing of patient waste and cleaning spills such custodial technicians.

Personal protective equipment as defined by USP <800> includes wearing two pairs of ASTM-tested chemotherapy gloves that have been evaluated for permeability, impervious gowns that close in the back, and head, hair, shoe and sleeve covers when compounding hazardous drugs. When compounding sterile products, the outside glove must be sterile. When nurses are administering hazardous drugs, they need only wear ASTM-tested chemotherapy gloves and an impervious gown, but they may require additional eye and face protection if splashing or aerosolization of the dosage form is possible. For further information regarding PPE use, USP <800> provides a table of various activities included in the hazardous drug handling process and the PPE required to be worn during those activities.

**Training for Compounding Personnel**

Pharmacies should put in place an adequate training program for employees who are compounding hazardous drugs. All training should occur prior to preparing hazardous drugs and at least every 12 months thereafter. Topics that are required to be communicated to compounding staff include: types of hazardous drugs and their risks, the health care systems’ policies and procedures, ordering, receiving, and stocking of HDs, proper hand hygiene, use of PPE, use of C-PECs and other equipment and devices, negative pressure techniques, safe aseptic practices, spill control and response to unintended exposure.

As far as training for physical compounding activities is concerned, the compounding supervisor should demonstrate specific processes and procedures to trainees and subsequently have the trainees complete the previously demonstrated processes without assistance from, but under the direct supervision of, the compounding supervisor. Following the initial training period, the compounding supervisor should continue to periodically evaluate the competency of all employees in relation to compounding processes and document accordingly.

**Cleaning**

The proposed chapter divides the cleaning process for hoods and other areas used for compounding hazardous drugs into four main steps: deactivation, decontamination, cleaning and disinfecting (see Table 2). It is necessary that employees who perform cleaning functions are protected from inadvertent exposure while carrying out their duties. Therefore, appropriate PPE should be worn while carrying out all cleaning operations. Pharmacies should clearly define their cleaning processes, the cleaning products and dilutions used, and the documentation strategies and requirements employed in their standard operating procedures.
### Table 2. Cleaning Guidelines for Hazardous Compounding Areas

<table>
<thead>
<tr>
<th>Cleaning Step</th>
<th>Appropriate Product or Action to be Taken</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Deactivation  | 2% Sodium Hypochlorite solution           | Sodium Hypochlorite will pit stainless steel  
Sodium Thiosulfate or germicidal detergent in sterile water should be used following Sodium Hypochlorite administration |
| Decontamination | Physical wiping of surface with low-lint wipe and one of the following:  
-Alcohol  
-Sterile water  
-Peroxide  
-Sodium Hypochlorite | Should occur:  
-At least weekly  
-Any time a spill occurs  
-Before and after certification  
-After voluntary interruption  
-If ventilation tool is removed |
| Cleaning      | Trivalent or Quadrivalent Detergent  
Peroxide       | Product shall not be toxic, volatile, corrosive or harmful to compounding surface |
| Disinfecting  | Sterile 70% Isopropyl Alcohol  
UV light       | Should occur:  
-At beginning of workday  
-Between batches  
-At beginning of each shift  
-Routinely during compounding  
-Any time after C-PEC has been turned off |

### Spill Control

Spills that occur at any point during the hazardous drug handling process should be addressed, contained and cleaned immediately so as to minimize unintended exposure. Appropriate PPE should be worn by those attending to spills and those individuals should be properly trained in spill management. Spill kits should be readily available in all areas where hazardous drug are handled on a routine basis. All spills should be properly documented.

If an employee attending to a spill becomes contaminated (direct skin or eye contact, unintended exposure to significant volumes of hazardous drugs without proper PPE donned, etc.) they should immediately receive medical attention. In addition, an incident report should be completed to document the exposure.

### Environmental Quality and Control

According to USP <800> recommendations, regular environmental sampling should take place so as to ensure complete containment of hazardous drugs within drug preparation areas. The work surface of the hood, countertops where hazardous items are placed, areas surrounding hoods (including floor below work area) and patient administration areas should undergo surface wipe sampling. Samples should then be assayed for presence of hazardous drug residue and if measurable contamination is present action such as evaluation of employee work practices, retraining, cleaning and evaluation of engineering controls should be taken. Ideally, sampling should occur at baseline and at least every six months thereafter.
Medical Surveillance

A medical surveillance program is required as part of the proposed chapter USP <800>. The program is intended to monitor employees in such a manner as to minimize harmful effects in those who may be exposed to hazardous drugs. All employees involved in any aspect of the hazardous drug handling process should be screened at baseline and on a regular basis thereafter for health status changes as they may relate to hazardous drug exposure. A medical surveillance program should ideally include all of the following:

- Establishment of a monitoring strategy (typically a questionnaire) for identifying employee exposure to hazardous drugs (drugs handled, hours spent handling drugs, number of preparations or administrations per week, etc.).
- A means for monitoring employee health at baseline (general health history, reproductive history, etc.) and periodically thereafter (typically this is accomplished via an annual questionnaire).
- Development of a program to obtain baseline clinical evaluations (laboratory values, physical examinations, etc.) and subsequent evaluations on a scheduled basis dictated by employee exposure and risk.
- A plan for addressing health status changes that have been identified through the medical surveillance program.

There are many ways an organization can design its medical surveillance program to include the aforementioned components. For example, a program implemented at Nebraska Methodist Hospital employed a tiered approach in which employees were screened for exposure to hazardous drugs and placed in various risk categories/tiers. The program was composed of four tiers:

- Tier 1 (low risk): Self-surveillance composed primarily of educational interventions and self-reporting of exposure and health changes.
- Tier 2 (medium risk): Employer/supervisor surveillance, which included all tier one activities as well as an annual basic physical exam, an annual reproductive questionnaire and trending of sick calls.
- Tier 3 (high risk): Comprehensive medical surveillance, which included all tier one and two activities as well as an annual comprehensive physical exam, complete blood count (CBC) with differential, complete urinalysis (UA), and liver function tests (LFTs) at baseline and annually thereafter.
- Tier 4: Post-exposure surveillance, which involved a comprehensive physical exam, monitoring of CBC with differential, UA and LFTs as well as a notation in the employee’s file documenting their exposure.

Regardless of the medical surveillance program design, if health changes are identified in exposed employees, the organization should take action by examining all engineering controls for containment efficiency, performing environmental sampling within engineering controls and evaluating the employee’s compliance with PPE and knowledge of the organizations policies and procedures related to hazardous drug handling. If deficiencies in equipment functionality or employee knowledge are noted, a plan of action should be developed to prevent future employee exposure. Various organizations such as the American Society of Health-System Pharmacists (ASHP), NIOSH and the Oncology Nursing Society (ONS) provide additional information regarding development of a proper medical surveillance program.
Overall, USP <800> builds on the recommendations set forth by USP <795> and <797> with specific recommendations put forth regarding hazardous drug handling in the health care setting. However, as opposed to the aforementioned chapters, which are exclusive to compounding operations, USP <800> spans the entire hazardous drug handling process. The proposed USP <800> chapter was open for public comment until July 31, 2014, and will subsequently be finalized taking all comments into consideration. Once published, the chapter will become official and enforceable six months following its publication date.

As this article is intended to provide a brief overview of USP <800>, it should be understood that this article is not all inclusive of the numerous recommendations put forth by USP. Health-system administrators and employees involved in the hazardous drug process should read USP <800> in its entirety and understand all requirements and recommendations set forth by the chapter. By providing additional guidelines for hazardous drug handling in the health care setting, the hope is that employee and environmental exposure will be limited to as low a limit as reasonably achievable and adverse health effects of those exposed will be minimized.

Continuing Education Self-assessment Questions

1. Which of the following negative health effects has been well documented in nurses exposed to antineoplastic drugs?
   a. Increased risk of lymphoma
   b. Increased risk of congestive heart failure
   c. Increased risk of spontaneous abortion
   d. Increased risk of stillbirth

2. Which of the following is not a characteristic used to define a hazardous drug?
   a. Genotoxicity
   b. Organ toxicity at high doses
   c. Carcinogenicity
   d. Teratogenicity

3. USP <800> compounding recommendations refer exclusively to sterile hazardous drug compounding.
   a. True
   b. False

STOP AND REFLECT
You are the pharmacy supervisor at a large health-system. As part of your organization’s medical surveillance program, a pharmacy technician completes an annual questionnaire to identify their level of hazardous drug exposure and document any health changes that they have experienced. The pharmacy technician identifies that they deliver chemotherapy to patient care areas daily and have had five spontaneous abortions while being employed in the organization. What is your response?
4. Hazardous drugs and nonhazardous drugs may be stored together as long as the hazardous drugs are in their final unit dose or unit-of-use packaging.
   a. True
   b. False

5. Which of the following is an unacceptable configuration for hazardous drug compounding?
   a. Compounding a sterile product in a Class II BSC contained in a segregated, non-negative pressure room
   b. Compounding a sterile product in a CACI contained in a segregated, negative pressure C-SCA that is not ISO 7 classified
   c. Compounding a nonsterile product in a CVE contained in a segregated, negative pressure room
   d. Compounding a nonsterile product in a Class II BSC that is dedicated to nonsterile product compounding contained in a segregated, negative pressure room

6. Compounding personnel are required to wear all of the following PPE components at all times except:
   a. Two pairs of ASTM-tested chemotherapy gloves
   b. Impervious gown
   c. Shoe covers
   d. N95 respirator

7. Which of the following statements is correct?
   a. CSTDs are required when compounding and highly recommended when administering hazardous drugs.
   b. CSTDs are highly recommended when compounding and required when administering hazardous drugs.
   c. CSTDs are highly recommended, but not required, when compounding and administering hazardous drugs.
   d. CSTDs are required when compounding and administering hazardous drugs.

8. Which one of the following is not a cleaning tactic when cleaning hazardous drug compounding areas?
   a. Decontamination
   b. Deactivation
   c. Sterilizing
   d. Cleaning

9. A medical surveillance program should be designed to:
   a. assess employee compounding accuracy and ability.
   b. monitor employee exposure to hazardous drugs and associated negative health effects.
   c. ensure employees are properly trained to compound hazardous drugs.
   d. confirm employee compliance with cleaning processes defined in the organization’s standard operating procedures.

10. Nonhazardous drug compounding may NOT take place in a containment primary engineering control that is dedicated to hazardous drug compounding.
    a. True
    b. False
References:


