

DISCUSSION GUIDE

An Update On Protecting Health Care Practitioners and Patients from Hazardous Drugs



Planned by **ASHP Advantage** and supported
by an educational grant from **BD**.



This continuing pharmacy education discussion guide is designed to provide pharmacists and technicians with an overview of the new proposed USP General Chapter <800> and explain the implications of the chapter for current policies and procedures in the health system. Faculty members are nationally recognized experts regarding federal regulations, accreditation standards, and state activities aimed at protecting health care workers from exposure to hazardous drugs.

The estimated time to complete this activity is 60 minutes. This activity is provided free of charge and is available from March 31, 2015, to March 30, 2016.

LEARNING OBJECTIVES

After participating in this knowledge-based educational activity, participants should be able to

- Describe trends in and the current rate of compliance of U.S. pharmacies with United States Pharmacopeia (USP) Chapter <797> standards for pharmaceutical compounding of sterile preparations, including hazardous drugs, and list common barriers to compliance
- Discuss current state regulations for sterile drug compounding as they relate to USP Chapter <797> standards, the legal enforceability of the standards, and recent state board of pharmacy activities related to sterile drug compounding to improve patient and health care worker safety
- Compare and contrast standards pertaining to hazardous drugs in USP Chapter <797> and proposed Chapter <800> on handling hazardous drugs in health care settings
- Define the ideal facility design elements for inpatient and ambulatory practice sites where hazardous drugs are prepared
- List the key changes in the upcoming revision to the 2004 National Institute for Occupational Safety and Health Alert on Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings, and recommend actions for health care organizations to take to ensure compliance with the recommendations in the updated Alert

TARGET AUDIENCE

This continuing pharmacy education activity was planned to meet the needs of health-system pharmacists and technicians, especially those who come in contact with hazardous drugs, are responsible for managing practitioners who work with hazardous drugs, and those who are interested in improving the safety of the health-system environment.

EXECUTIVE SUMMARY

The body of evidence of the adverse impact of exposure of health care workers to hazardous drugs has grown in recent years, leading to efforts to reduce this exposure through the development of up-to-date evidence-based standards and recommendations from authoritative groups and state regulations for protective measures. Complying with United States Pharmacopeia (USP) Chapter <797> standards for pharmaceutical compounding of sterile preparations, including hazardous drugs, often presents a challenge to pharmacy personnel because of limitations in financial resources, physical plant, training, time, and other factors. Improvements in compliance with USP Chapter <797> requirements for hazardous drug compounding have been observed over the past several years, but considerable room for improvement remains. State regulations for sterile drug compounding vary widely, and only about half of the states have regulations that specifically refer to USP Chapter <797> standards. The USP Chapter <797> standards are legally enforceable regardless of state regulations. A general Chapter <800> on the handling of hazardous drugs in health care settings is in development by USP, and it addresses nonsterile as well as sterile preparations.

The National Institute for Occupational Safety and Health (NIOSH) is in the process of updating the recommendations in its 2004 Alert on Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. Key changes to the Alert include elimination of the list of hazardous drugs from the 2004 Alert (Appendix A in that document) and creation of a separate list of hazardous drugs, which was released in September 2014 with plans for biennial updates. Other changes to the Alert include updates to the literature review and glossary, and inclusion of updated recommendations for ventilation controls, personal protective equipment, closed system drug-transfer devices, work practices, hazardous waste handling, and medical surveillance. New guidance will be provided on environmental surface wipe sampling to evaluate the effectiveness of efforts to prevent and contain workplace contamination, the use of robotics for handling hazardous drugs, and exposure of veterinary health care workers to hazardous drugs. The updated NIOSH Alert will be consistent with proposed USP Chapter <800>. The NIOSH recommendations are not legally enforceable. Health care organizations should assess their hazardous drug programs and lists of hazardous drugs to ensure that they are consistent with the new USP Chapter <800> and NIOSH hazardous drug list and Alert.

REVIEWERS AND DISCLOSURES

The assistance of the planners and reviewers of this educational activity is gratefully acknowledged.

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CURRENT STATUS

The safe handling of hazardous drugs has been a concern among health-system pharmacy personnel and others for decades. The issue was first formally addressed by ASHP in a technical assistance bulletin published in 1985, and it has come to the forefront again because of efforts by the United States Pharmacopeia (USP) to establish standards for proper handling of hazardous drugs in health care settings.^{1,2} A section on hazardous drug compounding was added to USP Chapter <797> on pharmaceutical compounding of sterile preparations in 2008. This USP Chapter <797>, the 2006 ASHP Guidelines on Handling Hazardous Drugs, the 2004 National Institute for Occupational Safety and Health (NIOSH) Alert on Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings, and other publicly-available documents were the foundation for the proposed USP general Chapter <800> on handling of hazardous drugs in health care settings.^{3,4}

A nationwide survey of sterile compounding practices and rates of compliance with USP Chapter <797> standards by pharmacies has been conducted annually since 2011. The 719 respondents to the most recent (2014) survey were from 45 states, the District of Columbia, Puerto Rico, and several Canadian provinces.⁵

The majority (525, or 73%) of pharmacies participating in the 2014 survey were hospital-based.⁵ Respondents in other settings included 76 home infusion pharmacies (11%), 40 community pharmacies (6%), 23 clinic pharmacies (3%), and 23 nuclear pharmacies (3%). Six central fill/outsource providers, three outsourcing facilities registered with the Food and Drug Administration (FDA), three veterinary pharmacies, and one office-based pharmacy also participated in the survey. Two thirds (67%) of all 719 survey respondents

reported that they handle hazardous drugs.⁵ A slightly higher percentage (71%) of the 525 respondents in hospital pharmacies handle hazardous drugs.

A variety of primary engineering controls, including a Class II biological safety cabinet (BSC) and compounding aseptic containment isolator (CACI), were used by survey respondents to prevent contamination of sterile preparations and protect health care workers and the environment from exposure to hazardous drugs.⁵ The most common approach was use of a combination of a laminar airflow workbench for nonhazardous drug compounding and a Class II BSC for hazardous drug compounding. A Class II BSC or CACI is required for compounding of sterile hazardous drugs, according to USP Chapter <797> and the proposed USP Chapter <800>.

In 2014, the self-reported rate of compliance with USP Chapter <797> requirements for pharmaceutical compounding of sterile preparations, which were implemented in 2003, was 81% among survey respondents.⁵ The rate of compliance varied among settings from 80% in hospital pharmacies, 81% in clinic pharmacies, and 82% in nuclear pharmacies to 88% in home infusion pharmacies, 89% in community pharmacies, 91% in FDA-registered outsourcing facilities, and 92% in central fill/outsource providers. The rate of compliance among hospitals tended to be higher in larger facilities than in smaller ones. These compliance figures may be exaggerated because they were self-reported. The figures reflect a need for improvement.

Only about half of the states have regulations for sterile drug compounding that specifically refer to USP Chapter <797>.⁶ Another couple of dozen states and the District of Columbia address sterile drug compounding but do not mention USP Chapter <797> in their regulations. Only a few states lack sterile compounding regulations.



Does your state have regulations for sterile drug compounding that specifically refer to USP Chapter <797>? If not, are there plans to develop such regulations? What factors hinder plans to promulgate regulations holding pharmacies accountable for meeting Chapter <797> standards?

Many state boards of pharmacy have focused their attention on sterile compounding in the past couple of years since the outbreak of fatal meningitis traced to contaminated injectable steroid products prepared by a compounding pharmacy in Massachusetts. Writing new regulations, updating standards, and conducting more rigorous inspections of pharmacies where sterile drug compounding takes place are among the recent actions taken by state boards of pharmacy around the country. In some states, the department of public health has been responsible for licensing and overseeing pharmacy operations in hospitals. The state boards of pharmacy are responsible for licensing the pharmacists who work in hospitals and inspecting pharmacy operations in other settings, including community, home infusion, and compounding pharmacies. Recently, state boards of pharmacy have been granted the authority to conduct inspections of hospitals, holding them accountable for meeting USP Chapter <797> standards. For example, the state boards of pharmacy in California, Florida, Minnesota, and Texas have been actively and aggressively conducting inspections and issuing sterile compounding licenses and notices of deficiencies to hospitals. These activities to improve the safety of sterile drug compounding will continue to increase, especially when USP Chapter <800> standards are implemented.

The rate of pharmacy compliance with USP Chapter <797> requirements for pharmaceutical compounding of sterile preparations increased from 73.9% in 2011

to 81.3% in 2014.⁵ This change reflects the increased attention to patient safety issues associated with sterile drug compounding by state boards of pharmacy and others. The rate of compliance with USP Chapter <797> requirements for hazardous drug compounding increased a small amount from 71.3% to 75.4% over the same period, reflecting increased attention to health care worker and environmental safety. However, the rate in 2014 leaves much room for improvement.

Surveys of sterile compounding practices recently became part of the certification process for critical access hospitals participating in Medicare. Inadequate training of surveyors on standards for safe compounding practices has been identified as a shortcoming of this process.⁷

Written confirmation by compounding employees of reproductive age (male or female) that they understand the risks of handling hazardous drugs is required in USP Chapter <797>. This requirement ensures that pharmacies comply with federal Occupational Safety and Health Administration (OSHA) hazardous communication standards (i.e., right-to-know laws). In 2011, the rate of compliance with this requirement in hospital pharmacies was 23.9%.⁸ In the 2014 survey, written confirmation was obtained in 42.3% of hospital pharmacies, a value that reflects a marked improvement, but further improvement is needed.⁵

According to USP Chapter <797>, hazardous drugs should be stored under negative pressure. However, this practice was reported by only 55% of hospital pharmacies participating in the 2014 survey.⁵

The rate of compliance among all survey respondents (i.e., including those in settings other than hospitals) with USP Chapter <797> requirements that employees who handle, dispose, or compound hazardous drugs must successfully complete a hazardous drug competency assessment prior to working with hazardous drugs and annually thereafter was 61.2% in 2014.⁵ Thus, there is considerable room for improvement in the training of employees who handle hazardous drugs.

Respondents to the 2014 survey of sterile compounding practices identified several barriers to compliance with USP Chapter <797> requirements (Table 1).⁵ Financial and budget restrictions, physical plant limitations, and training and competency resource availability were the most common barriers. Lack of leadership support and knowledge were unexpected factors associated with difficulty complying.

TABLE 1.

Primary Challenges to Compliance with USP Chapter <797> Requirements for Pharmaceutical Compounding of Sterile Preparations^{5,a}

Barrier	% of Respondents
Financial and budget restrictions	27
Physical plant limitations	21
Training and competency resource availability	19
Time required	16
Compounding staff resistance to change	7
Leadership lack of support	3
Leadership lack of knowledge	2

^a Challenges to compliance with USP Chapter <797> requirements for pharmaceutical compounding of sterile preparations were identified by 719 respondents to a 2014 survey of pharmacies in 45 states, the District of Columbia, Puerto Rico, and several Canadian provinces.



What barriers hinder the ability of your institution to comply with the hazardous drug handling requirements in USP Chapter <797> and in the proposed Chapter <800>? What steps could be taken to overcome these barriers?

REGULATION AND OVERSIGHT

All standards in USP general chapters numbered less than 1000, including the standards for pharmaceutical compounding of sterile preparations in Chapter <797>, standards for pharmaceutical compounding of nonsterile preparations in Chapter <795>, and standards for the handling of hazardous drugs in health care settings in the proposed Chapter <800>, are legally enforceable regulations. They are not merely guidelines. The Centers for Medicare and Medicaid Services recently recognized the USP chapters related to sterile and nonsterile compounding as authoritative minimum standards of safe practice for critical access hospitals.⁹

State regulations governing sterile drug compounding vary widely and are subject to frequent change in many states.⁶ USP Chapter <797> standards (and the proposed Chapter <800> standards) are legally enforceable under the Federal Food, Drug, and Cosmetic Act, regardless of state regulations.

The terminology used in USP chapters has important nuances, with “shall” or “must” used in statements about requirements and “should” used for recommended practices. The process for developing USP Chapter <800> is lengthy, with multiple opportunities for input from stakeholders and several revisions by an expert committee. The first draft was published in the May-June 2014 issue of *Pharmacopeial Forum*. Feedback from stakeholders was incorporated into the draft, and a new proposed chapter based on this feedback was posted online December 1, 2014, with a public comment period ending May 31, 2015.² Once final revisions are made, the chapter will be published in the *United States Pharmacopeia/National Formulary (USP/NF)*. Another 6 months or longer will elapse after publication of the chapter in the USP/NF before the standards become enforceable.

PROPOSED USP CHAPTER <800>

The USP Chapter <797> standards address hazardous drug receipt, storage, and compounding in the pharmacy—processes involved in drug handling up until administration of the drug begins.¹⁰ These standards are intended to protect pharmacy personnel from hazardous drug exposure. The scope of USP Chapter <800> is wider and encompasses processes beginning with receipt of the drug at the facility (e.g., the loading dock) through administration and disposal of the drug in various settings (e.g., oncology ward, ambulatory or specialty clinics, physician offices, surgical and procedural areas).² These standards are intended to protect patients and all of the personnel who come in contact with hazardous drugs in the facility (e.g., materials management and nursing personnel as well as pharmacy personnel).

Compliance with USP Chapter <797> requires compliance with all of the standards in the chapter, not just some of the standards. Compliance is analogous to listening to a symphony because all of the instruments in the orchestra are required for a successful performance. Selecting only certain musical instruments or “cherry picking” certain elements of the USP standards is inadequate. There is no such thing as partial compliance with USP Chapter <797> requirements. A facility is either in compliance or not in compliance.

The hazardous drug handling requirements in USP Chapter <797> address facilities (i.e., storage and compounding), personal protective equipment (PPE), staff orientation and training, and health care worker and environmental monitoring.¹⁰ The proposed Chapter <800> contains a number of new requirements. It was developed by compiling hazardous drug handling requirements from USP Chapter <797> and other authoritative sources (e.g., NIOSH, ASHP, Oncology Nursing Society [ONS], OSHA), taking into consideration expert consensus and stakeholder input.

Protecting patients from hazardous drugs has been and will remain a goal of USP standards. Data are gradually emerging to demonstrate the short- and long-term effects of exposure of health care workers to hazardous drugs (e.g., genotoxicity, reproductive risks), although additional data are needed to quantify the impact. Registries of health care workers with harm attributed to hazardous drug exposure have been established in a few states (e.g., Washington state). According to USP Chapter <797>, hazardous drugs “shall be prepared under conditions that protect health care workers and others in preparation and storage areas.”¹⁰ Protecting health care workers as well as patients from hazardous drugs also is among the USP Chapter <795> standards for pharmaceutical compounding of nonsterile preparations.¹¹ The proposed Chapter <800>, which encompasses both sterile and nonsterile hazardous drugs, emphasizes health care worker and environmental safety as well as patient safety.² The new USP Chapter <800> will complement but not replace Chapters <797> and <795>. Standards pertaining to hazardous drugs in Chapters <797> and <795> will be cross referenced with Chapter <800> instead of duplicating the standards. When proposed USP Chapter <800> is finalized, USP Chapters <797> and <795> will be harmonized (i.e., modified so that they are consistent) with Chapter <800>.

According to both USP Chapter <797> and proposed Chapter <800>, antineoplastic hazardous drugs requiring manipulation and hazardous drug active pharmaceutical ingredients must be stored separately from other inventory in a manner that prevents spillage or breakage if the container falls and contamination and health care worker exposure.² In the past, USP Chapter <797> stated that hazardous drugs should be stored in a negative-pressure room with external ventilation (i.e., exhausting of air through a high-efficiency particulate air filter to the exterior of the building where contaminants are diluted with fresh air) and at least 12 air changes per hour. These conditions are required in proposed Chapter <800>, not merely strongly recommended as in the past in Chapter <797>.²

This change reflects the fact that guidance documents addressing the storage of hazardous drugs have been available from other sources for a long time, so the feasibility of this requirement is well established.

According to USP Chapter <797>, sterile hazardous drug preparation must be performed in an environment with ISO Class 5 or better air quality (which is achieved using a primary engineering control, such as a Class II BSC or CACI) within a space with ISO Class 7 or better air quality that is physically separate from other activities (i.e., a clean room).¹⁰ A negative-pressure room, with pressure monitoring and external ventilation is recommended in Chapter <797>. Proposed Chapter <800> goes further to require the use of ISO Class 5 air quality within an ISO Class 7 physically-separate negative-pressure space with external ventilation for hazardous drug preparation.² Thus, what was recommended for hazardous drug preparation in Chapter <797> will be required in Chapter <800>.

An exemption to the recommendation to use a negative-pressure room has been permitted in Chapter <797> for facilities that prepare a low volume of hazardous drugs if a closed system drug-transfer device (CSTD) is used, although the volume considered low is not defined.² This exemption was eliminated from proposed Chapter <800> because of the potential for harm from contamination of health care workers and the work environment during even a small volume of compounding or storage or transport of hazardous drug components. Sterile hazardous drug preparation in a containment-segregated compounding area (C-SCA), such as a Class II BSC or CACI, in a clinic or satellite pharmacy instead of a clean room is permitted in proposed Chapter <800> for low- and medium-risk compounding if the product will be administered within 12 hours after preparation.² This time frame (i.e., beyond-use time) accommodates concerns about microbiological sterility. The C-SCA must be a separate room with a Class II BSC or CACI, negative pressure, external ventilation, and at least 12 air changes per hour, but it does not need to have ISO Class 7 or

better air quality. The provision for a C-SCA instead of an ISO Class 7 negative-pressure clean room for compounding sterile hazardous drugs has not been permitted in Chapter <797>. The changes in proposed Chapter <800> represent a concession by allowing the use of a C-SCA as long as the room is under negative-pressure and a short beyond-use time is assigned to the compounded sterile preparations.

According to proposed Chapter <800>, CSTDs should be used when compounding hazardous drugs (if the dosage form allows).² By contrast, these devices must be used when administering hazardous drugs (if the dosage form allows).

According to Chapter <797>, appropriate personal protective equipment (PPE) must be worn when handling hazardous drugs.¹⁰ Many health care workers fail to perceive a need for PPE when using a CACI, but Chapter <797> states that requirements for wearing gowns and other garb should be followed unless the CACI manufacturer can provide written documentation based on validated environmental testing that any components of PPE are not required. This PPE exemption was intended only for the handling of nonhazardous drugs. To date, no manufacturer has demonstrated that PPE is not required when handling or compounding hazardous drugs. Proposed Chapter <800> requires proper PPE to be worn while preparing hazardous drugs in a CACI. Standards for PPE in proposed Chapter <800> depend on the function performed and an assessment of risk. When chemotherapy gloves are required, they must meet American Society for Testing and Materials (ASTM) standard D6978, which addresses the resistance of glove materials to permeation by chemotherapy drugs.^{2,12} The gloves must be sterile and powder-free to avoid contaminating the work area with powder and adsorbing hazardous drugs. Gowns must be disposable and shown through testing not to be permeable to hazardous drugs.² Cloth gowns must not be worn because they can allow permeation of and skin exposure to hazardous drugs.

FACILITY DESIGN

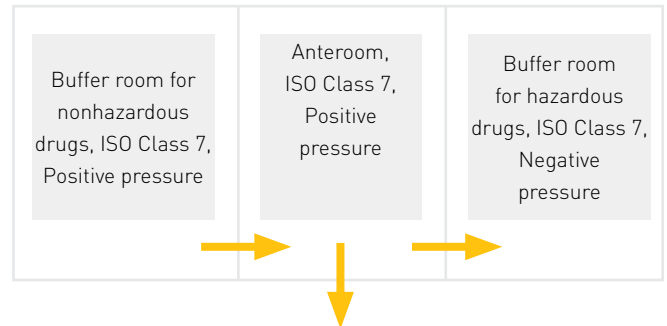
The key elements of facility design in health care organizations where sterile hazardous drugs are prepared include the use of a National Sanitation Foundation 49 certified Class II BSC or CACI that meets Controlled Environment Testing Association requirements and is located in a separate room under negative pressure, with external ventilation and the appropriate number of air changes per hour (12 for a C-SCA and 30 for an ISO Class 7 clean room). Use of these elements with appropriate PPE and environmental monitoring can protect health care workers, the environment, and patients from hazardous drugs.

A common facility design used in the inpatient pharmacy setting for hazardous drug preparation involves a positive-pressure ISO Class 7 anteroom with two adjoining ISO Class 7 buffer rooms, one under positive pressure for nonhazardous drugs and the other under negative pressure for hazardous drugs (Figure 1).² A common facility design used for hazardous drug preparation in oncology clinics has a positive-pressure ISO Class 7 anteroom, with a single adjoining ISO Class 7 negative-pressure buffer room for hazardous drug preparation (Figure 2). Once Chapter <800> becomes enforceable, a third facility design that could be used for compounding hazardous drugs in an inpatient C-SCA within an ISO-unclassified environment (i.e., the non-ISO classified clean room environment in proposed Chapter <800>) involves establishing a perimeter line around the ISO Class 5 containment-primary engineering control (Figure 3). This line creates a segregated compounding area so that hazardous drug preparation activities are separated from other types of activity conducted in a negative-pressure room.

The facility design must be taken into consideration when establishing policies and procedures for PPE. For example, two pairs of shoe covers must be worn in a negative-pressure buffer room where hazardous drugs are compounded, according to proposed USP Chapter <800>.² One pair of shoe covers is removed before leaving the hazardous drug buffer room to prevent the spread of hazardous drug contamination from the floor of the buffer room to spaces outside the buffer room.

Figure 1

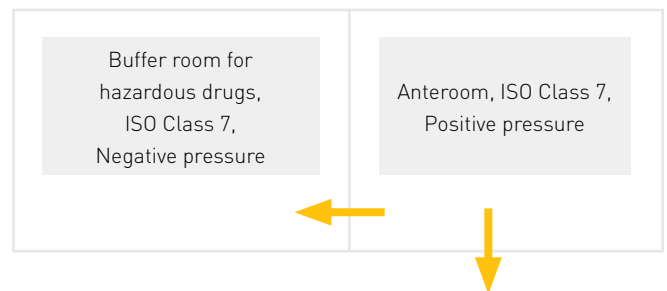
A common facility design for sterile hazardous drug preparation in an inpatient pharmacy setting^a



^aArrows indicate the direction of air flow.
Source = reference 2.

Figure 2

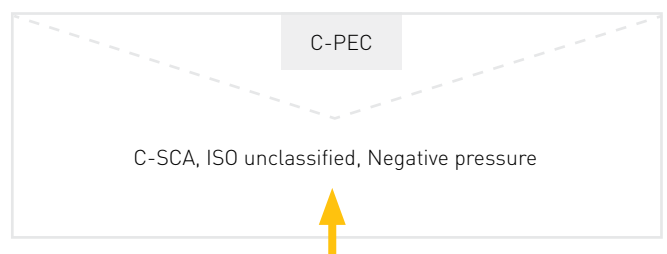
A facility design for sterile compounding of hazardous drugs in an oncology clinic^a



^aArrows indicate the direction of air flow.
Source = reference 2.

Figure 3

A facility design for preparing sterile hazardous drugs using a containment-primary engineering control (C-PEC) within a containment-segregated compounding area (C-SCA) in an ISO-unclassified environment^a



^aArrow indicates the direction of air flow.
Source = reference 2.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH ALERT

In 2004, NIOSH released an Alert on preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings.⁴ The document was the result of an extensive 4-year writing, review, and revision process by the nearly 40 members of the NIOSH Hazardous Drug Safety Working Group and additional stakeholders, including practitioners, academicians, representatives from pharmaceutical and equipment manufacturers, regulatory authorities, members of various organizations (e.g., ASHP, ONS, American Nurses Association) and labor unions. The 2004 Alert was subject to both internal NIOSH review and external review.

The 2004 Alert provides criteria for defining hazardous drugs, a list of examples of hazardous drugs (Appendix A of the Alert), and recommendations for safe handling of these agents. The hazardous drugs list in Appendix A of the Alert was compiled from information provided by four institutions that had generated lists of hazardous drugs for their respective organizations. The Pharmaceutical Research and Manufacturers of America also submitted a list. These lists were not reviewed against the NIOSH hazardous drug criteria at that time, but all drugs on the current NIOSH hazardous drug list have been reviewed since then using the criteria.

A revision of the Alert is in development, with plans to release it in late 2015 after extensive internal and external review and revision by NIOSH. The updated Alert will not include a hazardous drugs list. To provide a current list of hazardous drugs in a timely manner, NIOSH developed an independent review process to update the list biennially, resulting in a separate guidance document.¹³ The list of hazardous drugs is updated based on evaluation of data for new FDA-approved drugs and drugs with new FDA warnings. The list revision process is conducted by expert reviewers with input from stakeholders. Final decisions about additions to and deletions from the list are made by

NIOSH. The review process for the NIOSH list of hazardous drugs is described in the Federal Register.¹⁴ The 2014 NIOSH list of antineoplastic and other hazardous drugs in healthcare settings is available on the NIOSH website.¹³ This ongoing review process and stand-alone guidance document allow the omission of Appendix A from the update to the NIOSH Alert.

The criteria (i.e., characteristics) used by NIOSH to define a hazardous drug (Figure 4) are based on a definition developed by ASHP in 1990 that was subsequently amended and adopted by NIOSH in 2004.¹⁵ Exposure to mutagens, carcinogens, and teratogens has been a concern for a long time. Many agents recently added to the list of hazardous drugs are reproductive toxins (formerly classified in FDA pregnancy category D or X before the agency modified its approach to providing pregnancy, lactation, and reproductive information in product labeling), and many of these agents are commonly used in clinical practice (e.g., clonazepam, finasteride, fluconazole, paroxetine, warfarin).¹⁶

Exposure to genotoxins is a concern for health care workers. Genotoxicity, as exhibited by mutagenic changes in cells caused by antineoplastic drugs, was one of the earliest signs of occupational exposure studied in health care workers. In a landmark study published in 1979, Falck and colleagues used the then newly-developed Ames test to measure mutagens in the urine of oncology nurses.¹⁷ Genotoxicity was the primary criterion for defining hazardous drugs in the 1990 ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs in Hospitals.¹⁵ In modifying the 1990 ASHP criteria for defining hazardous drugs, NIOSH noted that when evaluating mutagenicity for potentially hazardous drugs, responses from multiple test systems are needed before precautions can be required for handling such drugs.⁴

All drugs cause toxicity but some drugs cause organ toxicity at low doses, and these agents are included in the NIOSH list of hazardous drugs.⁴ To assist in

Figure 4.NIOSH 2004 Characteristics of Hazardous Drugs^{4,a}

- **Carcinogenicity**
- **Teratogenicity or other developmental toxicity^b**
- **Reproductive toxicity^b**
- **Organ toxicity at low doses^b**
- **Genotoxicity^c**
- **Structure or toxicity of a new drug similar to that of established drugs previously classified as hazardous**

^aDrugs with one or more of these characteristics in humans or animals are considered hazardous.

^bAll drugs have toxic side effects, but some exhibit toxicity at low doses. The level of toxicity reflects a continuum from relatively nontoxic to production of toxic effects in patients at low doses (e.g., a few milligrams or less). For example, a daily therapeutic dose of 10 mg/day or a dose of 1 mg/kg per day in laboratory animals that produces serious organ toxicity, developmental toxicity, or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 µg/m³ after applying appropriate uncertainty factors. OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry. Under all circumstances, an evaluation of all available data should be conducted to protect health care workers.

^cIn evaluating mutagenicity for potentially hazardous drugs, responses from multiple test systems are needed before precautions can be required for handling such agents. The Environmental Protection Agency evaluations include the type of cells affected and in vitro versus in vivo testing.

interpreting the “low dose” description, the NIOSH Hazardous Drug Safety Working Group cited a series of publications authored by pharmaceutical industry toxicologists describing industry “performance” practices defining “low-dose” effects.⁴ In the pharmaceutical industry, occupational exposure limits based on laboratory animal toxicity are typically established for potent or toxic drugs.⁴ The low-dose criterion for organ toxicity in the definition of hazardous drugs (a daily therapeutic dose of 10 mg/day or a dose of 1 mg/kg/day in laboratory animals) is used as a benchmark.⁴

2014 NIOSH LIST OF HAZARDOUS DRUGS

Table 1 in the 2014 NIOSH list of hazardous drugs comprises antineoplastic drugs, including those with manufacturers’ safe handling guidance (MSHG), which usually is found in section 16 of the FDA-approved manufacturer’s package insert.¹³ Conjugated monoclonal antibody products that contain antineoplastic drugs (e.g., ado-trastuzumab emtansine, brentuximab vedotin) are included in this list based

on their American Hospital Formulary Service (AHFS) pharmacologic-therapeutic classification as 10:00 antineoplastic agents and the MSHG warning in section 16 of the FDA-approved product labeling noting that they require special handling and disposal as anticancer drugs.

Table 2 in the 2014 NIOSH list of hazardous drugs presents non-antineoplastic drugs that meet one or more of the NIOSH criteria for a hazardous drug, including those with MSHG.¹³ Ganciclovir, for example, is classified among AHFS 8:18:32 nucleosides and nucleotides, but it has an MSHG because the manufacturer considers the drug a potential teratogen and carcinogen in humans, which are two of the NIOSH criteria for defining hazardous drugs.

Table 3 in the 2014 NIOSH list of hazardous drugs includes non-antineoplastic drugs that primarily have adverse reproductive effects.¹³ This table will be updated when FDA implements its pregnancy and lactation labeling rule omitting the pregnancy letter categories A, B, C, D, and X in 2015.¹⁶ Table 4a lists

drugs deleted from the 2004 list (e.g., the antiviral agent vidarabine) because the NIOSH review panel determined that the drugs do not meet the NIOSH hazardous drug criteria. Table 4b lists only tetracycline, a drug deleted from the 2012 list on the basis of stakeholder comments.

Table 5 in the 2014 NIOSH list of hazardous drugs provides abbreviated guidance for the use of PPE (gloves, protective gown, and eye and respiratory protection) and ventilated engineering controls for working with hazardous drugs in health care settings.¹³ Recommendations for numerous possible scenarios with various drug formulations (e.g., tablets, capsules, liquids, powders), routes of administration (e.g., oral, inhalation, topical, injection), and actions (e.g., compounding, administering) are described. More detailed information on safe handling practices is available in the NIOSH 2004 Alert and proposed USP Chapter <800>.

The updated NIOSH Alert will be harmonized with proposed USP Chapter <800> and will include recommendations found in Table 5 in the 2014 NIOSH list of hazardous drugs. The containment requirements (e.g., use of primary engineering controls, PPE, and work practices) proposed in USP Chapter <800> must be followed for antineoplastic hazardous drugs that require manipulation and when handling hazardous drug active pharmaceutical ingredients appearing on the 2014 NIOSH list.² However, final antineoplastic hazardous drug dosage forms that do not require manipulation other than counting (e.g., tablets that are not crushed, capsules that are not opened) may not be subject to these containment requirements unless required by the manufacturer if the entity performs an assessment of risk and determines alternative containment strategies. An assessment of risk may be performed for dosage forms of other hazardous drugs (i.e., non-antineoplastic hazardous drugs in Table 2 of the 2014 NIOSH list of hazardous drugs, non-antineoplastic hazardous drugs with primarily adverse reproductive effects in Table 3 of the 2014 NIOSH list of hazardous drugs) to determine appropriate containment strategies and work practices

that protect the environment and health care workers from exposure. Annual reassessment of the risk of hazardous drug exposure is recommended by NIOSH to ensure that proper workplace protections are provided and followed.

NEW INFORMATION

The updated NIOSH Alert will include new evidence from the large volume of literature published since 2004 on surface contamination of the workplace with hazardous drug residue, health care worker exposure to hazardous drugs, and adverse health effects from that exposure. A substantial amount of research on worker exposure, including the measurement of hazardous drugs in the urine of exposed workers, has been conducted in the intervening years, primarily in Europe, Japan, and Canada and to a lesser extent in the United States. The lack of research in the United States presents a challenge when attempting to develop evidence-based guidelines for handling hazardous drugs.

Some of the new literature on hazardous drugs addresses exposure of home health care workers, patients, family members, and the environment in the home care setting. Handling of oral chemotherapy and proper disposal of contaminated human waste and linens are among the issues addressed in recent years. The NIOSH maintains a website with an [online bibliography of published articles](#) on occupational exposure to antineoplastic drugs and other hazardous drugs that is organized by topic and a second website with [links to all NIOSH documents on hazardous drug exposures in health care](#). These websites and other resources on the handling of hazardous drugs are listed in the Appendix to this discussion guide.

The updated NIOSH Alert will provide recommendations for ventilation controls, PPE, CSTDs, work practices (e.g., drug receipt, storage, and manipulation techniques), and hazardous waste handling. These recommendations will be consistent with USP Chapter <797> for sterile compounding and proposed Chapter <800>, and readers of the Alert will be referred to the USP chapters for specific details.

The recommendations for PPE in the updated Alert will be harmonized with Table 5 in the 2014 NIOSH list of hazardous drugs as well as USP Chapter <797> and proposed Chapter <800>. The updated Alert will discuss the differences between the ASTM standards for chemotherapy gloves (D6978) and the general ASTM standard for resistance of protective clothing materials to permeation (ASTM F739), which may be used for protective gowns.^{12,18,19} Guidance also will be provided on the use of gloves when handling solid oral and liquid non-antineoplastic hazardous drugs.

In the 2004 NIOSH Alert, the term “closed system drug-transfer device” was created as a generic term to describe the single device that was approved by FDA at that time for compounding hazardous drugs. In the Alert glossary, this device was defined as a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system.⁴ The acronym CSTD has been widely used in the literature, but it does not appear in the 2004 Alert. Considerable confusion has surrounded the interpretation of the NIOSH definition of the device. In response to an inquiry from European researchers about how their drug preparation system compares with the definition, NIOSH explained that “the Alert’s glossary was not really intended to be a specification guide for equipment design criteria. Rather, we sought to identify the desired function that the defined piece of equipment should provide. In the case of the CSTD, the intended function was to preserve the sterility of the product while preventing the escape of a hazardous drug, in whatever form it may exist, into the surrounding environment.”²⁰ According to NIOSH, “one of the problems with a definition that is not clearly based on performance criteria but rather implies a specific construction or design is that such definition will exclude other technical solutions with the same or better performance according to the specified criteria.”²⁰ No performance standard for the definition of CSTD has been developed by NIOSH or any other organization, including FDA. However, NIOSH has

created a test protocol using a surrogate to measure CSTD performance in a uniform test system. The document has undergone multiple internal and external reviews. Once the responses to the reviews have been considered, NIOSH will release the document for public comment.

Organizational decisions about selecting commercially-available CSTD products should be based primarily on effectiveness. However, input from nursing and pharmacy staff as well as other users of these products should be considered because different products or components may be preferred in different work settings,

The updated NIOSH Alert will provide guidance on all work practices addressed in the 2004 document based on recent research. For example, hazardous drug vials often arrive from the manufacturer with drug residue on the outside of the vial.^{21,22} In the past, pharmacy personnel have attempted to leverage their purchasing power and made grassroots efforts to place pressure on manufacturers to clean the vials prior to shipping, but recent drug shortages have reduced the opportunity to exert such leverage and limited the effectiveness of these grassroots efforts. Several manufacturers now provide vials covered in a plastic sheath, which reduces not only the transfer of contamination to health care workers and the environment but improves resistance of the vial to breakage. Research on cleaning techniques for contaminated vials without sheaths has found no procedure or cleaning solution to be highly effective.^{23,24}

Limited data are available from research conducted in the United States on improving work practices to contain contamination and prevent exposure of health care workers and patients because this research is costly with little financial return on investment. A recent review of the literature on safe handling of hazardous drugs identified only 16 papers originating from North America but 55 papers from Europe, which confirms that the United States is not at the forefront of this research.²⁵ The authors did not evaluate the reasons

for this disparity, but they noted that European work practices differ from those in North America and called for studies in North America to identify ways to best protect workers from occupational exposure to hazardous drugs. The updated NIOSH Alert will address problems related to work practices, present relevant research findings, and examine potential risk mitigation strategies related to work practices.

The hazardous waste handling information in the updated Alert will include relevant state and federal regulations and health care industry best practices. Because the current Environmental Protection Agency (EPA) regulations based on the Resource Conservation and Recovery Act (RCRA) of 1976 have not been significantly updated in more than 30 years, many drugs on the NIOSH hazardous drug list, especially newer agents used to treat cancer (drugs commonly known as “chemotherapy”), are at least as hazardous as those originally placed on the EPA P list and U list of hazardous chemicals.²⁶ Although the RCRA does not require hazardous waste disposal using specific color-coded containers, colors have been adopted by waste management services for practical purposes to make the process easier for facilities with large numbers of employees. The updated Alert will provide what are considered usual and customary terms for hazardous waste disposal.

Medical surveillance information in the updated NIOSH Alert will be harmonized with the proposed USP Chapter <800> and the 2012 NIOSH workplace solutions document on medical surveillance for health care workers exposed to hazardous drugs.²⁷ A substantial amount of surveillance work on reproductive risks from exposure to hazardous drugs has been performed by NIOSH in the past 10 years.^{28,29} Most of the work was conducted in nurses because of the large female population of these health care professionals. The updated Alert will reflect the findings from this research.

New guidance will be provided in the updated NIOSH Alert for cleaning of work surfaces and the use of environmental surface wipe sampling (i.e., the physical

retrieval of drug residue from a work surface for testing) to evaluate the effectiveness of efforts to prevent environmental contamination and work practices to deactivate hazardous drugs or decontaminate work surfaces. Assays are now available to identify and quantify numerous antineoplastic drugs.³⁰ Several companies market wipe sampling kits that include directions, collecting material, reagents, and shipping containers.³⁰ Drug assays are available that may be performed on a single wipe sample for a panel with a limited number of hazardous drugs, allowing a facility to conduct environmental surface wipe sampling and monitor for hazardous drug surface contamination. Although assays are not available for all hazardous drugs, information on the level of contamination with “marker” drugs in the panel may reflect the level of contamination with other hazardous drugs and the effectiveness of work practices to prevent and remove contamination. There are no accepted occupational exposure limits for hazardous drugs, but monitoring allows a baseline level of contamination to be established and the effectiveness of cleaning agents and work practices to be evaluated.

Many researchers have investigated the efficacy of various cleaning agents using surface wipe sampling, and some manufacturers of cleaning agents have tested their products for hazardous drug deactivation, removal, or both.³¹ Most cleaning agents tested do not necessarily deactivate a hazardous drug. They may, however, contain surfactants and other ingredients that remove hazardous drug contaminants. Cleaning products that have been shown to be effective for removing hazardous drug contaminants from work surfaces should be used for cleaning work surfaces where hazardous drugs are handled in addition to the disinfectants needed in sterile compounding areas. The updated NIOSH Alert will be harmonized with proposed USP Chapter <800>, identify new cleaning agents and surface wipe sampling methods, and address criteria for assessing the efficacy of analytical laboratories providing wipe sampling kits.

The updated NIOSH Alert will include an updated glossary, which is needed because of the proliferation of new terms and acronyms pertaining to hazardous drug handling since 2004. This glossary will be harmonized with terminology and acronyms used in proposed USP Chapter <800>.

The updated NIOSH Alert also will include two new sections on robotics and veterinary exposure. The latter was addressed by NIOSH in the 2010 workplace solutions document on safe handling of hazardous drugs for veterinary health care workers, and the updated Alert will be harmonized with that document.³² A discussion of large and small robots and other automated technology, including limitations as well as capabilities in handling hazardous drugs, will be included in the Alert.

IMPLICATIONS FOR HEALTH CARE ORGANIZATIONS

An NIOSH Alert is a document that provides guidance. Staff at a facility may be questioned by a state or federal OSHA inspector about practices that are not consistent with the recommendations in an Alert, but the recommendations are not legally enforceable standards.

Health care organizations must compare their hazardous drug safety program and list of hazardous drugs with the updated NIOSH Alert, 2014 NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, and proposed USP Chapter <800>. Revisions to organizational policies, procedures, and other hazardous drug program materials may be needed after performing this crosswalk and gap analysis to ensure that the organizational program is comprehensive and up-to-date.

The Centers for Medicare and Medicaid Services, state agencies, and accreditation organizations that survey hospitals are likely to place greater emphasis on the requirements and best practices for all sterile compounding activities in the future.⁷ For example, The Joint Commission (TJC) medication management standards require that health care organizations maintain a list of hazardous drugs, so surveyors will

expect to see a current list.³³ Surveyors will not accept the NIOSH list unless it has been adapted so that it is consistent with the organizational formulary.

Developing and updating hazardous drug handling policies and procedures should be an interdisciplinary effort. Input should be obtained from risk managers to protect the environment, health care workers, and patients.



Is your institution prepared for the release of the new USP standards on handling hazardous drugs and the updated NIOSH Alert on preventing occupational exposures to hazardous drugs? Do you have a list of hazardous drugs that you can share with surveyors from accreditation organizations, representatives from the state board of pharmacy, and OSHA inspectors? Are your organizational policies and procedures for handling hazardous drugs and other hazardous drug program materials consistent with the proposed USP Chapter <800> standards and the recommendations in the updated NIOSH Alert? What changes will you need to make to comply with the new USP standards and NIOSH recommendations?

CONCLUSION

Hazardous drug exposure poses a risk of harm to health care workers and patients. New standards from USP and recommendations from NIOSH for the safe handling of hazardous drugs are in development to reduce environmental contamination and occupational exposure. Health care organizations must be proactive in updating their hazardous drug programs to make them consistent with the new USP standards and NIOSH recommendations and minimize the risk of hazardous drug exposure and harm to health care workers and patients.

APPENDIX - RESOURCES ON HANDLING HAZARDOUS DRUGS

American Society of Health-System Pharmacists

ASHP guidelines on compounding sterile preparations (2014) [View Guideline](#) (PDF)

ASHP guidelines on handling hazardous drugs (2006) [View Guideline](#) (PDF)

ASHP technical assistance bulletin on compounding nonsterile products in pharmacies (1994) [View Bulletin](#)

The Joint Commission

Improving patient and worker safety: opportunities for synergy, collaboration and innovation (Appendix A provides OSHA topics matched to Joint Commission standards as of January 2012) [View Resource](#)

National Institute for Occupational Safety and Health

NIOSH alert: preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings (2004, with obsolete Appendix A, which should not be used) [View Alert](#) (PDF)

NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2014 [View List](#) (PDF)

Occupational exposure to antineoplastic agents (bibliography of published articles arranged by topic) [View Resource](#)

Hazardous drug exposures in health care (links to NIOSH documents on hazardous drugs) [View Resource](#)

Safe handling of hazardous drugs for veterinary healthcare workers (2010) [View Resource](#) (PDF)

Personal protective equipment for health care workers who work with hazardous drugs (2008) [View Resource](#) (PDF)

Medical surveillance for healthcare workers exposed to hazardous drugs (2012) [View Resource](#) (PDF)

NIOSH current intelligence bulletin: reproductive risks associated with hazardous drug exposures in healthcare workers and recommendations for reducing exposures (2015) [View Resource](#)

Oncology Nursing Society

Safe handling of hazardous drugs, 2nd ed (2011) [View Resource](#)

Safe handling of cytotoxic agents [View Resource](#)

Occupational Safety and Health Administration

OSHA Hazard Communication: OSHA Standards [View Resource](#)

OSHA Technical Manual (OTM). Section VI: Chapter 2:

Controlling Occupational Exposure to Hazardous Drugs (currently in revision) [View Resource](#)

The United States Pharmacopeia

Briefing: <800> hazardous drugs—handling in healthcare settings. December 1, 2014. [View Resource](#) (PDF)

<797> Pharmaceutical compounding—sterile preparations. In: USP compounding compendium (2015) [View Resource](#)

<795> Pharmaceutical compounding—nonsterile preparations. In: USP compounding compendium (2015)

[View Resource](#)

CONTINUING EDUCATION CREDIT INFORMATION

Once you have read the discussion guide (an assessment test is provided below as a study aid only), click on the link below to take the online assessment test (minimum score 70%) and complete your evaluation. Continuing pharmacy education (CPE) credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of completion of a home study activity.



The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1 hour (0.1 CEU, no partial credit) of continuing pharmacy education credit (ACPE activity # 0204-0000-15-425-H03-P and 0204-0000-15-425-H03-T).

Take Test and Process CPE**ASSESSMENT TEST STUDY AID**

This assessment test is provided as a study aid only. Follow the instructions above to complete this assessment test and the evaluation online to obtain CE credit for this activity.

- In 2014, the self-reported rate of compliance with USP Chapter <797> requirements for pharmaceutical compounding of sterile preparations among U.S. hospital pharmacies was approximately**
 - 40%.
 - 60%.
 - 80%.
 - 90%.
- Which of the following changes in the rate of compliance with USP Chapter <797> requirements for hazardous drug compounding was observed between 2011 and 2014?**
 - A small increase from a low 2011 rate to a 2014 rate that leaves much room for improvement.
 - A small increase from a high 2011 rate to a 2014 rate that leaves little room for improvement.
 - A small decrease from a high 2011 rate to a 2014 rate that leaves some room for improvement.
 - A large increase from a low 2011 rate to a 2014 rate that leaves little room for improvement.
- The proportion of the states with regulations for sterile drug compounding that specifically refer to USP Chapter <797> standards is best characterized as**
 - Very few states.
 - About a dozen states.
 - Roughly half of all states.
 - The vast majority of states.
- Which of the following was the most commonly reported barrier to compliance with USP Chapter <797> requirements for pharmaceutical compounding of sterile preparations in a 2014 survey of pharmacies?**
 - Compounding staff resistance to change.
 - Financial and budget restrictions.
 - Leadership lack of knowledge.
 - Time required.

5. Which of the following items related to hazardous drug compounding and handling are legally enforceable?
- (A) Both USP standards and NIOSH recommendations.
 - (B) USP standards but not NIOSH recommendations.
 - (C) NIOSH recommendations but not USP standards.
 - (D) Neither USP standards nor NIOSH recommendations.
6. Which of the following statements about USP Chapter <797> and proposed Chapter <800> standards for hazardous drug storage in a negative-pressure room with external ventilation and at least 12 air changes per hour is correct?
- (A) These conditions have been only strongly recommended in Chapter <797> but will be required in Chapter <800>.
 - (B) These conditions have been required in Chapter <797> but will be only strongly recommended in Chapter <800>.
 - (C) These conditions have been and will continue to be required in Chapter <797> and will be required in Chapter <800>.
 - (D) These conditions have been and will continue to be only strongly recommended in Chapter <797> and will be only strongly recommended in Chapter <800>.
7. An exemption to the strong recommendation in USP Chapter <797> to use a negative-pressure room for hazardous drug compounding is permitted in proposed USP Chapter <800> if:
- (A) A high volume of hazardous drugs is prepared at the facility, and a containment-segregated compounding area is used.
 - (B) A low volume of hazardous drugs is prepared at the facility, and a closed system drug-transfer device is used.
 - (C) An ISO Class 5 or better air quality with external venting and at least 30 air changes per hour is provided.
 - (D) A containment-segregated compounding area is used, and the product will be administered within 12 hours after preparation.
8. Which of the following is among the key elements of facility design in health care institutions where hazardous drugs are prepared?
- (A) A closed system drug-transfer device that meets American Society for Testing and Materials standards.
 - (B) A negative-pressure ISO Class 7 anteroom.
 - (C) A certified Class II biological safety cabinet in a negative-pressure buffer room.
 - (D) A laminar airflow workbench in a negative-pressure buffer room.

9. A large number of which of the following were added to the 2014 National Institute for Occupational Safety and Health list of antineoplastic and other hazardous drugs in healthcare settings?
- (A) Carcinogens.
 - (B) Genotoxins.
 - (C) Reproductive toxins.
 - (D) Teratogens.
10. The National Institute for Occupational Safety and Health created a stand-alone list of antineoplastic and other hazardous drugs in health care settings and will remove Appendix A when they update the 2004 Alert on preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings because the list:
- (A) Was too long and cumbersome.
 - (B) Needed to be updated more frequently than the Alert.
 - (C) Became legally unenforceable.
 - (D) Contained a large number of agents that needed to be removed.
11. Which of the following will be a new topic in the upcoming revision to the National Institute for Occupational Safety and Health (NIOSH) Alert on preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings and requires harmonization with a 2010 NIOSH workplace solutions document on the topic?
- (A) Cleaning.
 - (B) Medical surveillance.
 - (C) Robotics.
 - (D) Veterinary exposure.
12. Which of the following statements about the use of closed system drug-transfer devices when handling hazardous drugs is correct based on the proposed USP Chapter <800>?
- (A) The devices must be used for compounding and when administering hazardous drugs.
 - (B) The devices should be used for compounding and when administering hazardous drugs.
 - (C) The devices must be used for compounding and should be used when administering hazardous drugs.
 - (D) The devices should be used for compounding and must be used when administering hazardous drugs.

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