

Safe Handling Of Hazardous Drugs: Reviewing Standards for Worker Protection

**LUCI A. POWER,
MS, RPH**

*Senior Pharmacy Consultant
Power Enterprises
San Francisco, California*

**MARTHA POLOVICH,
PHD, RN, AOCN**

*Associate Director
Clinical Practice
Duke Oncology Network
Durham, North Carolina*



The year 2010 marked 4 decades of concern for health care workers exposed to cytotoxic and other hazardous drugs.¹ As a new generation of health care workers joins those already engaged in patient care, it is essential that they understand the occupational risks associated with the handling of hazardous drugs and the need for training in proper techniques for all handling activities to reduce occupational exposure to such drugs. Continuing research in this area, promoted by the National Institute for Occupational Safety and Health (NIOSH), demonstrates ongoing exposure.

Hazardous drugs, including antineoplastic agents, antiviral agents, biological modifiers, hormones, and other agents, provide therapeutic benefit to patients, but studies have shown that healthy workers exposed to these drugs may experience adverse effects.²⁻⁴ Potential health risks for workers who compound and administer these agents include adverse reproductive outcomes

and cancer.⁵ This review emphasizes new information about this well-recognized issue. It focuses on NIOSH's activities as well as the 2008 revision of United States Pharmacopeia (USP) Chapter <797>, which mandates compliance with environmental, engineering, and training standards for worker as well as product protection.

Routes of Occupational Exposure

Many studies have documented both surface and worker contamination from hazardous drugs.⁶⁻¹³ Standard work practices for handling injectable drugs in vials and syringes generate powder and liquid aerosols. These drug residues may contaminate the air and surfaces in the work area.^{6-8,14,15} It also has been shown that many hazardous drug vials are delivered from the manufacturer with drug residue on the outside of the vials, creating yet another opportunity for contamination.¹⁶ Certain hazardous drugs have been shown to vaporize at room temperature, resulting in drug contamination in the air.¹⁷⁻¹⁹ Workers may breathe contaminated air or touch contaminated surfaces and absorb hazardous drugs. Drug uptake also may occur through the ingestion of contaminated food or drink that is inappropriately located in or near drug-handling areas. Additionally, the transfer of contaminated residues from hands to mouth may result in the ingestion of hazardous drugs. Needlesticks with hazardous drug-contaminated needles or cuts from glass fragments of vials or ampules also may result in exposure by injection.

Guidelines for Safe Handling Of Hazardous Drugs

Since 1980, numerous organizations have issued guidelines for the safe handling of hazardous drugs. The Occupational Safety and Health Administration (OSHA) issued guidelines in 1986,²⁰ updated them in 1995,²¹ and made them available online in 1999.²² The American Society of Health-System Pharmacists (ASHP) published guidelines on the safe handling of cytotoxic agents as Technical Assistance Bulletins in 1985 and 1990, and new guidelines on hazardous drugs in 2006.²³⁻²⁵ In an attempt to influence nursing practice and protect its members from exposure, the Oncology Nursing Society (ONS) published guidelines for safe handling and also developed an extensive educational program based on “Chemotherapy and Biotherapy Guidelines and Recommendations for Practice.”²⁶⁻²⁸

Continuing Exposure

Adverse health effects and chances for exposure have been demonstrated among health care workers for more than 2 decades. Studies of surface and worker contamination conducted in the late 1990s and the early years of the following decade continued to document exposure.^{6-8,10,14,15} Some possible reasons for the problem include new workers’ lack of awareness of the issue, a lack of vigilance in work practices, poor adherence

to the use of personal protective equipment (PPE),²⁹⁻³² and other potential sources of contamination that have yet to be discovered.³³

In 2000, NIOSH convened a working group of interested individuals to examine the issue of occupational exposure of health care workers to hazardous drugs. The Hazardous Drug Safe Handling Working Group was composed of representatives from government (OSHA, NIOSH, and FDA), industry, pharmaceutical manufacturers, academia, membership organizations (eg, American Nurses Association, ASHP, and ONS), and union leaders whose members handle hazardous drugs. The Working Group assessed existing information and formulated a plan to increase affected workers’ awareness of the risks and to reduce those risks.

In 2004, as a result of the efforts of the Working Group, NIOSH issued “Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings.”³⁴ This NIOSH Alert is similar to the OSHA documents in that it is a guidance document without enforcement authority. However, OSHA may enforce the recommendations in the NIOSH Alert and the OSHA Technical Manuals under the general duty clause of the Occupational Safety and Health (OSH) Act, which sets safety and health standards for US workers. Employers subject to the OSH Act have a general duty to provide work and a workplace free from recognized, serious hazards.³⁵ Additionally, NIOSH actively continues to increase awareness of this issue by maintaining 2 Safety and Health Topic pages online: “Hazardous Drug Exposures in Health Care”³⁶ and “Occupational Exposure to Antineoplastic Agents.”³⁷ These pages provide links to extensive background information, the latest studies, updates on related activities, and NIOSH publications.

In 2007, the USP released Chapter <797>, “Pharmaceutical Compounding—Sterile Preparations,” which became effective in 2008.³⁸ This revision of the 2004 standard includes a section specific to the compounding of hazardous drugs and is coordinated with much of the 2004 NIOSH Alert. More importantly, USP Chapter <797> is an enforceable standard and establishes many of the NIOSH recommendations as requirements. The standards set by USP Chapter <797> are applicable in all settings in which sterile doses of hazardous drugs are compounded, not just hospitals and clinics.

To assess the impact of the 2004 NIOSH Alert on hazardous drugs, NIOSH designed a large, multifacility study to provide a comprehensive evaluation of the workplace and the potential sources of exposure.

Table 1. Comparison of 2004 NIOSH and 1990 ASHP Definitions

NIOSH	ASHP
Carcinogenicity	Carcinogenicity in animal models, in the patient population, or both, as reported by the International Agency for Research on Cancer
Teratogenicity or developmental toxicity	Teratogenicity in animal studies or in treated patients
Reproductive toxicity	Fertility impairment in animal studies or in treated patients
Organ toxicity at low doses	Evidence of serious organ or other toxicity at low doses in animal models or treated patients
Genotoxicity	Genotoxicity (ie, mutagenicity and clastogenicity in short-term test systems)
Structure and toxicity profile of new drugs that mimic existing drugs determined hazardous by the above criteria	

ASHP, American Society of Health-System Pharmacists; NIOSH, National Institute for Occupational Safety and Health
Originally published in reference 25 © 2006, American Society of Health-System Pharmacists, Inc. All rights reserved.
Reprinted with permission. (R1010)

Published in 2010, the study included surface sampling in pharmacy and nursing areas, self-maintained exposure diaries, and urine and blood sampling of various health care workers.³⁹ Consistent with the results of previous studies, the NIOSH study detected contaminated surfaces in all study sites. The findings of the study included a correlation between the size and spatial design of the compounding area and the amount of surface contamination. Preliminary reports support the USP Chapter <797> design standard that requires an appropriate buffer area around the primary engineering control (PEC).³⁸ The study site with a smaller, less delineated compounding area had greater surface contamination. Surprisingly, the percentage of surfaces contaminated with hazardous drug residue in this study is almost identical to that found in a similar study published in 1999.³³ In both studies, 75% of surfaces sampled in the pharmacies evaluated were found to have residue of at least one of the marker hazardous drugs. This apparently shows that the efforts of NIOSH and USP have made little difference.

Similar results of another study were presented at the Safe Handling of Hazardous Drugs in the Clinical Environment Symposium in Massachusetts in October

2009 and at the ASHP Midyear Clinical Meeting in Las Vegas in December 2009, by members of the Massachusetts General Hospital (MGH) Hazardous Drug Safety Task Force.^{40,41} At these meetings, the findings of an extensive, longitudinal study designed to assess contamination from receipt of the hazardous drug (loading dock) to hazardous waste transport (loading dock) were presented. The MGH Task Force identified a “chain of custody” for hazardous drugs and found surface contamination in most of the study areas along this chain, including on elevator buttons. According to the MGH investigators, another round of surface wipes will be conducted to assess interventions prior to publication of the study results.

These reports are not surprising, but they are alarming. Additional concern was generated by a substudy within the NIOSH research. In the companion study, also published in 2010, investigators at the University of Maryland evaluated chromosomal effects of the hazardous drugs studied to determine specific effects in the health care workers involved in the study.⁴² Therapy-related malignancies (myelodysplastic syndrome and acute myeloid leukemia) are known to be associated with signature lesions in chromosomes 5, 7,

and 11 based on fluorescence in situ hybridization. In the study, the DNA of exposed workers showed a statistically significant increased frequency of damage to chromosome 5 or 7 ($P=0.01$) and an increased frequency of damage to chromosome 5 alone ($P=0.01$). These results provide additional evidence for valid concerns regarding occupational exposure to hazardous drugs.

Barriers

Although many studies document continuing hazardous drug contamination and worker exposure, few have attempted to identify why the efforts to improve worker safety have not been successful. A recent research study with nurses sought to explain this issue. The purpose of the study was to examine relationships among factors affecting nurses' use of hazardous drug safe-handling precautions and to identify factors that promote or interfere with use of hazardous drug precautions. Using a cross-sectional, correlational design, 165 nurses from oncology centers across the United States who reported handling chemotherapy completed a mailed survey. Instruments measured use of hazardous drug precautions and various factors thought to influence the use of precautions. Despite the fact that nurses were knowledgeable about high chemotherapy exposure, total precaution use during administration and disposal of these drugs was low. Higher use of precautions was predicted by fewer patients per day per nurse, fewer barriers (eg, availability and convenience of PPE), and a better workplace safety climate (eg, training provided, supervisors encourage precaution use, and expectations that policies are followed). This has important implications because factors in the workplace environment seem to be the most important concepts affecting safe-handling practices.⁴³

Defining Hazardous Drugs

A number of drug types that are potent and toxic to patients have the potential to cause adverse effects in persons exposed to them occupationally. Although the cytotoxic potential of the alkylating agents is of primary concern, there are multiple mechanisms by which drugs exhibit hazardous effects. In 1990, ASHP attempted to categorize these drugs in its "Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs,"²⁴ for the first time using the term "hazardous drug" in reference to drugs that involve risks from occupational exposure. The terminology was selected to be inclusive of the types of drugs with safety

concerns and to be compatible with the then newly developed OSHA Hazard Communication Standard (HCS).^{44,45} The HCS is intended to ensure that employers and workers who are at risk for exposure to hazardous chemicals in the workplace are informed of the specific hazardous chemicals, their associated health and safety hazards, and the appropriate protective measures to be taken.

The HCS defines a "hazardous chemical" as any chemical that poses a physical or health hazard. It further defines a "health hazard" as any chemical for which statistically significant evidence from at least one study conducted in accordance with established scientific principles is available to indicate that it may cause acute or chronic health effects in exposed employees. The HCS further notes that the term "health hazard" includes chemicals that are carcinogens, toxic or highly toxic agents, reproductive toxins, irritants, corrosives, sensitizers, and agents that produce target organ effects.

ASHP has used similar criteria to define hazardous drugs.^{24,25} Data on the side effects of a drug are collected during both the drug's premarket investigational phase and clinical use. These data reasonably may be used to infer "health hazards" in workers occupationally exposed to the drug. As such, ASHP proposed the following criteria to define hazardous drugs²⁴:

- genotoxicity (ie, mutagenicity and clastogenicity in short-term test systems);
- carcinogenicity in animal models, in the patient population, or both, as reported by the International Agency for Research on Cancer;
- teratogenicity or fertility impairment in animal studies or in treated patients; and
- evidence of serious organ or other toxicity at low doses in animal models or treated patients.

ASHP's criteria for hazardous drugs were revised by NIOSH for the 2004 Hazardous Drug Alert. Table 1 compares the 2004 NIOSH and 1990 ASHP definitions of hazardous drugs. USP Chapter <797> has adopted the following definition of hazardous drugs, which supports both the HCS and the NIOSH Alert definitions: Drugs are classified as hazardous if studies in animals or humans indicate that exposures to them have a potential to cause cancer, developmental or reproductive toxicity, or harm to organs.³⁸

NIOSH has adopted a mechanism both to review its hazardous drug criteria and to judge newly FDA-approved drugs against these criteria on a regular basis. The review process for the addition of the

Table 2. Comparison of the NIOSH, ASHP, and USP Chapter <797> Recommendations for the Hazardous Drug Compounding Environment

	NIOSH	ASHP	USP Chapter <797>
Storage environment	Store hazardous drugs separately from other drugs in an area with sufficient general exhaust ventilation to dilute and remove any airborne contaminants.	Segregate hazardous drug inventory and store in an area with sufficient general exhaust ventilation to dilute and remove any airborne contaminants.	Hazardous drugs shall be stored separately from other inventory, preferably within a containment area such as a negative-pressure room.
Compounding	Prepare hazardous drugs in an area that is devoted to that purpose alone and is restricted to authorized personnel.	Hazardous drugs should be compounded in a controlled area where access is limited to authorized personnel trained in handling requirements.	Hazardous drugs shall be prepared in a PEC, which shall be placed in an ISO class 7 area that is physically separated from other preparation areas.
Ventilation	Where feasible, exhaust 100% of the filtered air to the outside.	Because of the hazardous nature of these preparations, a contained environment where air pressure is negative relative to that of the surrounding areas or that is protected by an air lock or anteroom is preferred.	<i>Storage:</i> area should have exhaust ventilation of at least 12 air changes per hour. <i>Compounding:</i> optimally at negative pressure relative to adjacent positive-pressure ISO class 7 or better ante-areas.

ASHP, American Society of Health-System Pharmacists; ISO, International Organization for Standardization; NIOSH, National Institute for Occupational Safety and Health; PEC, primary engineering control; USP, United States Pharmacopeia
Based on references 25, 34, and 38.

new listings is described in the *Federal Register*.⁴⁶ In 2007, a group of experts met to review the drugs that had been approved by the FDA since 2004 to evaluate which ones should be considered hazardous. Additionally, drugs that the FDA approved between 2007 and 2010 were recently evaluated for their hazardous characteristics. Following a rigorous review process, 21 drugs from many different therapeutic categories met at least one criterion of the hazardous definition in the analysis and have been added to the NIOSH list of hazardous drugs. The updated list was published in 2010, and is available, along with a discussion of hazardous criteria and instructions for generating a similar list of drugs for a given facility, on the NIOSH Web site.⁴⁷ This list supersedes the 2004 list in Appendix A.

Recommendations

Recommendations for the safe handling of hazardous drugs have been available since the early 1980s. As more research has been conducted and more groups have been involved, the recommendations have been coordinated in an attempt to provide uniformity. Each group, however, has a somewhat different focus. The NIOSH Alert and OSHA Technical Manuals are broad guidelines; the ONS “Chemotherapy and Biotherapy Guidelines” focus on administration and patient safety information; ASHP addresses pharmacists’ concerns; and USP Chapter <797> deals exclusively with sterile compounding.

All guidelines agree that to reduce exposure to hazardous drugs in the occupational setting, a comprehensive

Table 3. Comparison of NIOSH, ASHP, and USP Chapter <797> Recommendations for Primary Engineering Controls

	NIOSH	ASHP	USP Chapter <797>
Primary engineering controls	<ul style="list-style-type: none"> • Aseptic containment ventilation control class II BSC-type B2 is preferred. • Class III BSC or CACI. 	<ul style="list-style-type: none"> • Class II BSC-type B2 with outside exhaust is preferred. • Total exhaust is required if the hazardous drug is known to be volatile. • Class III BSC or CACI. 	<ul style="list-style-type: none"> • BSC or CACI that meets or exceeds the standards for CACI in USP Chapter <797>.
Ventilation	<ul style="list-style-type: none"> • Do not use a ventilated cabinet that recirculates air inside the cabinet or exhausts air back into the room environment if a drug is volatile. 	<ul style="list-style-type: none"> • Without special design considerations, class II BSCs are not recommended in traditional, positive-pressure clean rooms. 	<ul style="list-style-type: none"> • BSCs and CACIs optimally should be 100% vented to the outside air through HEPA filtration.

ASHP, American Society of Health-System Pharmacists; **BSC**, biological safety cabinet; **CACI**, compounding aseptic containment isolator; **HEPA**, high-efficiency particulate air; **NIOSH**, National Institute for Occupational Safety and Health; **USP**, United States Pharmacopeia
Based on references 25, 34, and 38.

safety program must be developed that deals with all aspects of drug handling—from selection and receipt of the product to storage, compounding, administration, spill control, and waste management. Key components of such a program are administrative controls, environmental and engineering controls, work practice controls, and PPE. These components are based on principles of industrial hygiene that have been successfully used to mitigate risks from other occupational exposures.⁴⁸

Administrative Controls

Administrative controls include policies, procedures, staff education and training, validation of competency, and medical surveillance. All aspects of hazardous drug handling must be identified, staff performance expectations clearly defined, methods for validating staff competency determined, and processes for the ongoing monitoring of adherence to policies judiciously established.

USP Chapter <797> emphasizes administrative controls for the safe compounding of hazardous drugs by mandating conditions that protect health care workers and other personnel in preparation and storage areas. Further requirements include extensive training of all personnel who handle hazardous drugs in the storage, handling, and disposal of such drugs. USP Chapter

<797> reinforces the OSHA and NIOSH recommendations by requiring training before the preparation or handling of hazardous compounded sterile preparations, and by mandating that the effectiveness of training be verified by testing specific hazardous drug preparation techniques. Ongoing training must be documented at least annually. The components of the training program are specified to include didactic overview of hazardous drugs and their mutagenic, teratogenic, and carcinogenic properties. The training program must address each new hazardous drug that enters the marketplace. Training in work practices also must include the following: aseptic manipulation; negative-pressure technique; correct use of safety equipment; containment, clean-up, and disposal procedures for breakages and spills; and treatment of personnel for contact and inhalation exposure.

OSHA and NIOSH include medical surveillance in their safety program recommendations. Medical surveillance involves collecting and interpreting data to detect changes in the health status of working populations potentially exposed to hazardous substances. In 2007, NIOSH released “Workplace Solution: Medical Surveillance for Health Care Workers Exposed to Hazardous Drugs,” which provides direction for establishing such a program and the elements that should be included.⁴⁹

Table 4. Comparison of NIOSH, OSHA, ASHP, And USP Chapter <797> Recommendations for PPE

	NIOSH/OSHA	ASHP	USP Chapter <797>
General handling	<ul style="list-style-type: none"> • Use double gloving for all activities involving hazardous drugs. <p>OSHA:</p> <ul style="list-style-type: none"> • Protective equipment, including PPE for eyes, face, head, and extremities, protective clothing, respiratory devices, and protective shields and barriers shall be provided, used, and maintained in a sanitary and reliable condition wherever it is necessary by reason of hazards of processes or environment, chemical hazards, radiological hazards, or mechanical irritants encountered in a manner capable of causing injury or impairment in the function of any part of the body through absorption, inhalation, or physical contact. 	<ul style="list-style-type: none"> • Wear double gloves for all activities involving hazardous drugs. • Guidelines for the safe handling of hazardous drugs recommend the use of gowns for compounding in the BSC, administration, spill control, and waste management to protect the worker from contamination by fugitive drug generated during the handling process. 	<ul style="list-style-type: none"> • Hazardous drugs shall be handled with caution at all times with the use of appropriate chemotherapy gloves during receiving, distributing, stocking, taking inventory, preparing for administration, and disposal.
Receiving and storage	<ul style="list-style-type: none"> • Wear chemotherapy gloves, protective clothing, and eye protection when opening containers to unpack hazardous drugs. 	<ul style="list-style-type: none"> • Gloves must be worn at all times when drug packaging, cartons, and vials are handled, including during the performance of inventory control procedures and the gathering of hazardous drugs. 	
Compounding	<ul style="list-style-type: none"> • Wear PPE (including double gloves and protective gowns) while reconstituting and admixing drugs. • Make sure that gloves are labeled as chemotherapy gloves. • Use disposable gowns made of polyethylene-coated polypropylene material (which is nonlinting and nonabsorbent). 	<ul style="list-style-type: none"> • Select disposable gowns of material tested to be protective against the hazardous drugs to be used. • Coated gowns must not be worn for longer than 3 hours during compounding and must be changed immediately when damaged or contaminated. • Gowns worn as barrier protection in the compounding of hazardous drugs must never be worn outside the immediate preparation area. 	<p>Sterile compounding:</p> <ul style="list-style-type: none"> • Shoe covers, head and facial hair covers (eg, beard covers in addition to face masks), and face masks; a nonshedding gown that has sleeves that fit snugly around the wrists and is enclosed at the neck; sterile powder-free gloves. <p>Hazardous drug compounding:</p> <ul style="list-style-type: none"> • Appropriate PPE shall be worn during compounding in a BSC or CACI and during the use of CSTDs. PPE should include gowns, face masks, eye protection, hair covers, shoe covers or dedicated shoes, double gloving with sterile chemotherapy-type gloves, and compliance with manufacturers' recommendations when a CACI is used.
Administration	<ul style="list-style-type: none"> • Wear PPE (including double gloves, goggles, and protective gowns) for all activities associated with drug administration. 	<ul style="list-style-type: none"> • Gowns worn during administration should be changed when the patient care area is left and immediately if contaminated. 	

ASHP, American Society of Health-System Pharmacists; **BSC**, biological safety cabinet; **CACI**, compounding aseptic containment isolator; **CSTD**, closed-system drug-transfer device; **OSHA**, Occupational Safety and Health Administration; **NIOSH**, National Institute for Occupational Safety and Health; **PEC**, primary engineering control; **PPE**, personal protective equipment; **USP**, United States Pharmacopeia
Based on references 22, 25, 34, and 38.

USP Chapter <797> requires that all compounding personnel with reproductive capability confirm in writing that they understand the risks associated with handling hazardous drugs. Although USP Chapter <797> mandates this only for personnel responsible for compounding, prudent practice dictates that the requirement should extend to all personnel who handle hazardous drugs along the chain of custody.

Environmental and Engineering Controls

The recent revision to USP Chapter <797> contains extensive mandates to improve the environment in which sterile doses of hazardous drugs are compounded. These directives are designed to increase safety for patients by reducing the potential for the microbial contamination of sterile dosage forms, and to improve worker safety by addressing design concerns in traditional, positive-pressure compounding environments. Table 2 compares the NIOSH, ASHP, and USP Chapter <797> recommendations for the environment in which hazardous drugs are compounded.

Hazardous drugs must be stored separately from other inventory in a manner to prevent contamination and exposure of personnel. Because of the concerns of volatilization at room temperature, storage is preferably within a containment area such as a negative-pressure room with sufficient exhaust ventilation and at least 12 air changes per hour (ACPH) to dilute and remove airborne contaminants.

An International Organization for Standardization (ISO) class 5 PEC is required for hazardous drug compounding to prevent microbial contamination of sterile preparations and to protect workers and the environment by preventing the escape of hazardous drug aerosols or residue. Appropriate PECs for compounding sterile hazardous drug preparations include class II biological safety cabinets (BSCs) and compounding aseptic containment isolators (CACIs) meeting or exceeding the standards set forth in USP Chapter <797>.

Isolators are recommended as a PEC in both the NIOSH Alert and the ASHP hazardous drug guidelines. The USP Chapter <797> revision sets performance standards for isolators used to compound sterile preparations, for compounding aseptic isolators (CAIs), and for isolators used to compound sterile hazardous drug preparations (CACIs). To meet the criteria of USP Chapter <797>, an isolator must provide isolation from the room and maintain ISO class 5 air quality within the cabinet during dynamic operating conditions. CAI and CACI air quality must be documented by particle counts

during compounding operations and during material transfer in and out of the isolator. Recovery time to ISO class 5 air in the main chamber must be documented after material is transferred into and out of the main chamber. Work practices must be developed to reduce disruption of the air quality in the isolator and to minimize recovery time.

A CACI meeting all of these conditions, as detailed in USP Chapter <797>, is exempt from the requirement of placing the CACI in an ISO class 7 buffer area. For hazardous drug compounding, however, the compounding area must maintain negative pressure and have a minimum of 12 ACPH.

A class II BSC has an open front and depends on an air barrier to prevent hazardous drug contamination from escaping the cabinet.⁵⁰ This air barrier can be compromised by worker technique, allowing escape of the contaminated air.⁵¹ The design of this type of cabinet is questionable for product protection because the air barrier is composed of air coming from the buffer area around the BSC. As air is pulled into the BSC, poor air quality in the buffer area may compromise the ISO class 5 compounding environment within the class II BSC. A class II BSC or CACI not meeting the conditions listed in USP Chapter <797> must be placed in an area that is physically separated from other compounding areas and have air quality of ISO class 7. Optimally, this area should be at negative pressure relative to adjacent positive-pressure ISO class 7 or better ante-areas, thus providing inward airflow to contain airborne drug. It also is optimal for a PEC used for compounding sterile hazardous drug preparations to be 100% vented to the outside air through high-efficiency particulate air (HEPA) filtration.

All environments in which sterile preparations are compounded must be provided with HEPA-filtered air from outside the environment. The PEC may not be the sole source of HEPA-filtered air and it may not provide more than 50% of the ACPH in that environment. The ISO class 7 buffer area and ante-area must be supplied with HEPA-filtered air providing at least 30 ACPH. Table 3 compares the NIOSH, ASHP, and USP Chapter <797> recommendations for hazardous drug PECs.

Work Practice Controls

Work practices must be designed to minimize the generation of hazardous drug contamination and maximize the containment of inadvertent contamination that occurs during routine handling or in the event of a spill. The compounding techniques described by Wilson

and Solimando continue to be the standard for any procedure in which needles and syringes are used to manipulate sterile dosage forms of hazardous drugs.⁵² These techniques, when performed accurately, minimize the escape of drugs from vials and ampules.

Many adjunct devices have been developed to reduce the generation of contamination during the compounding process. Vented needles with 0.2-micron hydrophobic filters were designed to reduce the powder and liquid drug residues that escape from vials through standard vented needles. Dispensing pins with small spikes and hydrophobic filters were introduced to make the compounding process more efficient. One study documents the effectiveness of one of these devices, but the investigators used only a visual inspection process because no sensitive drug assays were available at the time of the study.⁵³

Since then, sensitive, drug-specific assays have been developed that provide a means to validate work practice controls at different work sites. The persistent presence of contamination in hospitals and pharmacies generated interest in an adjunct device, generically named by NIOSH in the 2004 Alert as a “closed-system drug-transfer device” (CSTD). NIOSH defines a CSTD as one that mechanically prevents the transfer of environmental contaminants into the system and the escape of hazardous concentrations of drug or vapor from the system.³⁴ These systems provide some of the benefits of the earlier devices, but with the added protection that they can be locked into place on the drug vial. CSTD components also provide protection during the administration of IV push and IV infusion doses, which had not been available previously.

Numerous studies using markers for hazardous



drugs have demonstrated the effectiveness of a CSTD in reducing hazardous drug contamination in the workplace.^{6,14,15} At clinical practice sites representing inpatient and outpatient compounding and administration, the implementation of a CSTD reduced surface contamination significantly compared with standard practice.^{6,14,15}

USP Chapter <797> similarly defines CSTDs as “vial-transfer systems that allow no venting or exposure of hazardous substance to the environment.” USP Chapter <797> further states that CSTDs must be used within the ISO

class 5 environment of a BSC or CACI. In facilities that prepare a low volume of hazardous drugs, the use of 2 tiers of containment (eg, a CSTD within a BSC or a CACI that is located in a non-negative-pressure room) is acceptable. The NIOSH Alert specifies that CSTDs should be used only within a ventilated cabinet.

Neither USP Chapter <797> nor NIOSH has developed performance standards for any device marketed as a CSTD. Because the configurations of available CSTDs vary from that of the tested device, it is unclear how effective these devices are in reducing environmental contamination resulting from the compounding and administration of hazardous drugs. Any device marketed as a CSTD should be clinically tested.

Personal Protective Equipment

In addition to environmental and engineering controls, PPE is required to provide a barrier between the health care worker and the hazardous drug during episodes of potential contact. This is especially important during administration, spill control, handling of drug waste, and handling of patient waste because no PECs are in place for these activities. All PPE should be selected for effectiveness. Glove and gown materials should be able to withstand permeation by a selection of hazardous drugs.⁵⁴⁻⁵⁶ Several hazardous drugs require nonaqueous diluents for patient use and may permeate PPE more readily than others. The American Society for Testing and Materials has developed a standard for testing chemotherapy gloves.⁵⁷ There is no standard for testing chemotherapy gowns, but recommendations have been made based on several studies.^{55,56} See Table 4 for a comparison of PPE recommendations.

During sterile compounding, barrier garments must be worn to prevent the shedding of human skin and hair cells and the deposition of mucus or respiratory residue into the compounding area. USP Chapter <797> specifies that compounding garb must include the following: dedicated shoes or shoe covers, face masks, head and facial hair covers (eg, beard covers in addition to face masks), a nonshedding gown that has sleeves that fit snugly around the wrists and is enclosed at the neck, and sterile powder-free gloves.

Appropriate PPE must be worn when the sterile compounding of hazardous drugs is performed in a BSC or CACI and when CSTDs are used. PPE includes coated gowns, masks or respirators, eye protection, hair covers, shoe covers, and double gloving with sterile hazardous drug-tested gloves.

New Technologies

Technological advances include robotic automation that can compound sterile doses of hazardous and non-hazardous drugs. By replacing the human compounder, these robots reduce the occupational exposure of health care workers during the compounding process. Robotic units provide contained ISO class 5 environments and use techniques to reduce the generation of hazardous drug residues during compounding. Robots operate with sophisticated mechanics and software and provide a degree of accuracy and patient safety not available with manual compounding. CytoCare from Health Robotics, and RIVA (Robotic IV Automation) from Intelligent Hospital Systems provide robotic solutions to the compounding of sterile preparations

of hazardous drugs.

Like most technology, these robots are not perfect. They require human staff to load and clean them. Hazardous drug contamination may be generated in the compounding environment and transferred to the final product. Cleaning of the compounding environments requires both disinfection as well as decontamination of hazardous drug residues. No particular cleaner has been shown to effectively deactivate all known hazardous drugs,¹¹ so routine cleaning and spill control are still challenges to the health care personnel working with these robots. The robots help only with the compounding process, leaving the workers administering hazardous drugs without protection. Spill control and waste handling also remain issues for human workers to address.

Conclusion

Despite more than 3 decades of data on the adverse health effects of occupational exposure to hazardous drugs, skepticism about the risks continues, as evidenced by the lack of programmatic controls for reducing exposure. NIOSH has renewed its dedication to this health risk by continuing to promote worker awareness of safety. USP Chapter <797> has elevated many of the NIOSH recommendations to a standard, ensuring both awareness and compliance with at least the compounding segment of safety program controls.

Each new generation of health care workers needs to be educated about the risks of handling hazardous drugs and the importance of training in the proper techniques to reduce their exposure. Employers and employees must implement all aspects of hazardous drug safety programs to reduce occupational exposure and its potential adverse effects.

References

1. Ng LM, Jaffe N. Possible hazards of handling antineoplastic drugs. *Pediatrics*. 1970;46(4):648-649.
2. Crudi CB, Stephens BL, Maier P. Possible occupational hazards associated with the preparation/administration of antineoplastic agents. *NITA*. 1982;5(4):264-265.
3. Baker ES, Connor TH. Monitoring occupational exposure to cancer chemotherapy drugs. *Am J Health Syst Pharm*. 1996;53(22):2713-2723.
4. Sessink PJ, Bos RP. Drugs hazardous to healthcare workers. Evaluation of methods for monitoring occupational exposure to cytostatic drugs. *Drug Saf*. 1999;20(4):347-359.
5. Martin S. The adverse health effect of occupational exposure to hazardous drugs. *Community Oncol*. 2005;2(5):397-400.

6. Wick C, Slawson MH, Jorgenson JA, Tyler LS. Using a closed-system protective device to reduce personnel exposure to antineoplastic agents. *Am J Health Syst Pharm.* 2003;60(22):2314-2320.
7. Nygren O, Lundgren C. Determination of platinum in workroom air and in blood and urine from nursing staff attending patients receiving cisplatin chemotherapy. *Int Arch Occup Environ Health.* 1997;70(3):209-214.
8. Pethran A, Schierl R, Hauff K, Grimm CH, Boos KS, Nowak D. Uptake of antineoplastic agents in pharmacy and hospital personnel. Part I: monitoring of urinary concentrations. *Int Arch Occup Environ Health.* 2003;76(1):5-10.
9. Sessink PJ, Van de Kerkhof MCA, Anzion RB, Noordhoek J, Bos RP. Environmental contamination and assessment of exposure to antineoplastic agents by determination of cyclophosphamide in urine of exposed pharmacy technicians: is skin absorption an important exposure route? *Arch Environ Health.* 1994;49(3):165-169.
10. Sessink PJ, Boer KA, Scheefhals AP, Anzion RB, Bos RP. Occupational exposure to antineoplastic agents at several departments in a hospital. Environmental contamination and excretion of cyclophosphamide and ifosfamide in urine of exposed workers. *Int Arch Occup Environ Health.* 1992;64(2):105-112.
11. Dorr RT, Alberts DS. Topical absorption and inactivation of cytotoxic anticancer agents in vitro. *Cancer.* 1992;70(4 suppl):983-987.
12. Ensslin AS, Huber R, Pethran A, et al. Biological monitoring of hospital pharmacy personnel occupationally exposed to cytostatic drugs: urinary excretion and cytogenetics studies. *Int Arch Occup Environ Health.* 1997;70(3):205-208.
13. Sessink PJ, Wittenhorst BCJ, Anzion RB, Bos RP. Exposure of pharmacy technicians to antineoplastic agents: reevaluation after additional protective measures. *Arch Environ Health.* 1997;52(3):240-244.
14. Vandembroucke J, Robays H. How to protect environment and employees against cytotoxic agents, the UZ Ghent experience. *J Oncol Pharm Pract.* 2001;6(4):146-152.
15. Harrison BR, Peters BG, Bing MR. Comparison of surface contamination with cyclophosphamide and fluorouracil using a closed-system drug transfer device versus standard preparation techniques. *Am J Health Syst Pharm.* 2006;63(18):1736-1744.
16. Connor TH, Sessink PJ, Harrison BR, et al. Surface contamination of chemotherapy drug vials and evaluation of new vial-cleaning techniques: results of three studies. *Am J Health Syst Pharm.* 2005;62(5):475-484.
17. Connor TH, Shults M, Fraser MP. Determination of the vaporization of solutions of mutagenic antineoplastic agents at 23 and 37 degrees C using a desiccator technique. *Mutat Res.* 2000;470(1):85-92.
18. Opiolka S, Schmidt KG, Kiffmeyer TK, Schoppe G. Determination of vapor pressure of cytotoxic drugs and its effects on occupational safety. *J Oncol Pharm Pract.* 2000;6:15. Abstract.
19. Kiffmeyer TK, Kube C, Opiolka S, et al. Vapour pressures, evaporation behaviour and airborne concentrations of hazardous drugs: implications for occupational safety. *Pharm J.* 2002;268:331-337.
20. Yodaiken RE, Bennett D. OSHA work-practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. Occupational Safety and Health Administration. *Am J Hosp Pharm.* 1986;43(5):1193-1204.
21. Occupational Safety and Health Administration. Controlling occupational exposure to hazardous drugs. OSHA Technical Manual (OSHA Instruction CPL 2-2.20B CH-4). Washington, DC: Directorate of Technical Support, Occupational Safety and Health Administration; 1995:chap 21.
22. Occupational Safety and Health Administration. Controlling occupational exposure to hazardous drugs. OSHA Technical Manual (TED 01-00-015 [TED 1-0.15A] Sec VI Chap 2); 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html. Accessed February 16, 2011.
23. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic drugs in hospitals. *Am J Hosp Pharm.* 1985;42(1):131-137.
24. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm.* 1990;47(5):1033-1049.
25. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm.* 2006;63(12):1172-1191.
26. Brown KA, Esper P, Kelleher LO, O'Neil JEB, Polovich M, White JM, eds. *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice*. Pittsburgh, PA: Oncology Nursing Society; 2001.
27. Polovich M, White JM, Kelleher LO, eds. *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice*. 2nd ed. Pittsburgh, PA: Oncology Nursing Press; 2005.
28. Polovich M, Whitford JM, Olsen M, eds. *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice*. 3rd ed. Pittsburgh, PA: Oncology Nursing Press; 2009.
29. Martin S, Larson E. Chemotherapy-handling practices of outpatient and office-based oncology nurses. *Oncol Nurs Forum.* 2003;30(4):575-581.
30. Nieweg R, de Boer M, Dubbleman R, et al. Safe handling of antineoplastic drugs. Results of a survey. *Cancer Nurs.* 1994;17(6):501-511.
31. Valanis B, McNeil V, Driscoll K. Staff members' compliance with their facility's antineoplastic drug handling policy. *Oncol Nurs Forum.* 1991;18(3):571-576.
32. Valanis B, Vollmer WM, Labuhn K, Glass A, Corelle C. Antineoplastic drug handling protection after OSHA guidelines. Comparison by profession, handling activity, and work site. *J Occup Med.* 1992;34(2):149-155.
33. Connor TH, Anderson RW, Sessink PJ, Broadfield L, Power LA. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health Syst Pharm.* 1999;56(14):1427-1432.
34. National Institute for Occupational Safety and Health. Preventing occupational exposure to antineoplastic and other hazardous drugs in health care settings. DHHS (NIOSH) Publication No. 2004-165. Washington, DC: NIOSH; 2004. <http://www.cdc.gov/niosh/docs/2004-165/>. Accessed February 16, 2011.
35. Code of Federal Regulations. Title 29—Labor. Subtitle B—Regulations Relating to Labor. Chapter XVII—Occupational Safety and Health Administration, Department of Labor. Part 1910—Occupational Safety and Health Standards. Subpart A—General. Article 1910.2—Definitions. Washington, DC: US Government Printing Office; 2004. http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=/ecfrbrowse/Title29/29cfr1910_main_02.tpl. Accessed February 16, 2011.

36. National Institute for Occupational Safety and Health. NIOSH safety and health topic: hazardous drug exposures in health care. <http://www.cdc.gov/niosh/topics/hazdrug>. Accessed February 16, 2011.
37. National Institute for Occupational Safety and Health. NIOSH safety and health topic: occupational exposure to antineoplastic products. <http://www.cdc.gov/niosh/topics/antineoplastic/>. Accessed February 16, 2011.
38. US Pharmacopeial Convention. Chapter <797> Pharmaceutical compounding—sterile preparations. In: The United States Pharmacopeia, 31st rev, and The National Formulary, 26th ed. Rockville, MD: US Pharmacopeial Convention; 2008.
39. Connor TH, DeBord DG, Pretty JR, et al. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. *J Occup Environ Med*. 2010 Oct;52(10):1019-1027.
40. Demonaco HJ. Report on the Massachusetts General Hospital Hazardous Drug Study. Presented at: Safe Handling of Hazardous Drugs in the Clinical Environment Symposium; October 23, 2009; Bedford, MA.
41. Ahmed S. Massachusetts General Hospital (MGH) study of hazardous drug (HD) work practices: Study design and results. Presented at: American Society of Health-System Pharmacists Midyear Clinical Meeting; December 6-10, 2009; Las Vegas, NV.
42. McDiarmid MA, Oliver MS, Roth TS, Rogers B, Escalante C. Chromosome 5 and 7 abnormalities in oncology personnel handling anticancer drugs. *J Occup Environ Med*. 2010;52(10):1028-34.
43. Polovich, M. (2010). Nurses Use of Hazardous Drug Safe Handling Precautions. Unpublished doctoral dissertation.
44. Occupational Safety and Health Administration. Hazard Communication-59:6126-6184. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=federal_register&p_id=13349. Accessed February 16, 2011.
45. Occupational Safety and Health Administration. Hazard Communication Standard 1910.1200. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10099. Accessed February 16, 2011.
46. National Institute for Occupational Safety and Health. Hazardous drug alert. NIOSH Docket No. 105-A. Washington, DC: NIOSH; 2009. <http://www.cdc.gov/niosh/docket/archive/docket105A.html>. Accessed February 16, 2011.
47. National Institute for Occupational Safety and Health. NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2010. <http://www.cdc.gov/niosh/docs/2010-167/>. Accessed February 16, 2011.
48. US Department of Labor. 1998. OSHA 3143. Informational booklet on industrial hygiene. <http://www.osha.gov/Publications/OSHA3143/OSHA3143.htm>. Accessed February 16, 2011.
49. National Institute for Occupational Safety and Health. Medical surveillance for healthcare workers exposed to hazardous drugs. NIOSH Publication No. 2007-117. <http://www.cdc.gov/niosh/docs/wp-solutions/2007-117/>. Accessed February 16, 2011.
50. NSF International. NSF/ANSI 49-2007: NSF 49 Class II (Laminar Flow) Biosafety Cabinetry. Ann Arbor, MI: NSF International; 2007.
51. Clark RP, Goff MR. The potassium iodide method for determining protection factors in open-fronted microbiological safety cabinets. *J Appl Bacteriol*. 1981;51(3):439-460.
52. Wilson JP, Solimando DA Jr. Aseptic technique as a safety precaution in the preparation of antineoplastic agents. *Hosp Pharm*. 1981;16(11):575-576, 579-581.
53. Hoy RH, Stump LM. Effect of an air venting filter device on aerosol production from vials. *Am J Health Syst Pharm*. 1984;41(2):324-326.
54. Connor TH. Permeability of nitrile rubber, latex, polyurethane, and neoprene gloves to 18 antineoplastic drugs. *Am J Health Syst Pharm*. 1999;56(23):2450-2453.
55. Harrison BR, Kloos MD. Penetration and splash protection of six disposable gown materials against fifteen antineoplastic drugs. *J Oncol Pharm Pract*. 1999;5(2):61-66.
56. Connor TH. An evaluation of the permeability of disposable polypropylene-based protective gowns to a battery of cancer chemotherapy drugs. *Appl Occup Environ Hyg*. 1993;8:785-789.
57. American Society for Testing and Materials. D 6978-05 standard practice for assessment of resistance of medical gloves to permeation by chemotherapy drugs. West Conshohocken, PA: American Society for Testing and Materials; 2005.

Suggested Reading

Polovich M, Whitford JM, Olsen M, eds. *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice*. 3rd ed. Pittsburgh, PA: Oncology Nursing Press; 2009.

Connor TH, DeBord DG, Pretty JR, et al. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. *J Occup Environ Med*. 2010;52(10):1019-1027.

McDiarmid MA, Oliver MS, Roth TS, Rogers B, Escalante C. Chromosome 5 and 7 abnormalities in oncology personnel handling anticancer drugs. *J Occup Environ Med*. 2010;52(10):1028-1034.