Safe Handling of Hazardous Chemotherapy Drugs in Limited-Resource Settings

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1. Background

The toxic effects of antineoplastic drugs used for cancer treatment have been well known since their introduction in the 1940s. However, beyond the patient safety concerns arising from the necessary therapeutic use of these drugs, the occupational risks to health care workers handling these drugs in the course of their duties still need to be fully addressed.

Worldwide, more than 11 million new cases of cancer are diagnosed each year, and that number is expected to rise to 16 million by 2020 (WHO 2005). Treatment for many of these cases relies principally upon antineoplastic chemotherapy (Chabner et al. 1996). With approximately 100 different antineoplastic drugs now in use (NIOSH 2004, 2012) and many more under development, chemotherapy has opened new avenues, providing remission from the disease and the possibility of a cure in some cases. Addressing the formidable toxicity of these drugs, however, has been an ongoing challenge for clinicians and, more recently, for the occupational health community.

Over the last 20 years, an international consortium of content experts in occupational health, hospital pharmacy, and oncology nursing have combined their respective insights into a harmonized body of recommended practices for the safe transport, compounding, administration, and disposal of hazardous chemotherapy drugs (OSHA 1999; ISOPP 2007; Polovich 2011; ASHP 2006; NIOSH 2004). All these documents recommend a combination of hazard controls that include (1) engineering solutions to physically isolate the worker from drug exposure, to the extent possible; (2) administrative controls and work practices that further minimize drug contact through a designated organization of work, specialized worker training, and specified methods used to perform work tasks; and (3) use of personal protective equipment and apparel to minimize drug contact with the skin or respiratory tract.

These exposure control methods are applied in a specified order of preference, as listed above. This hierarchy reflects the relative degree of protection each method provides. In the United States of America, the European Union, and certain other regions, applying this combination of controls in the order listed is the recognized standard of professional practice for handling chemotherapy and other hazardous drugs (NIOSH 2004; CEC 1990; ISOPP 2007).

In low-resource countries, where the more costly engineering solutions such as biologic safety cabinets may be prohibitively expensive, there is necessarily an overreliance on the other elements of the hazard control hierarchy. Identifying dedicated areas for hazardous chemotherapy drug storage and compounding, restriction of personnel access to these areas, meticulous adherence to work practices that minimize drug aerosol production and work environment contamination, together with painstaking attention to worker training and skills assessment are the most reasonable set of alternatives to the internationally recognized best-practices approach described above.

This monograph describes in detail the rationale for and approaches to implementation of these alternative approaches to safe handling of hazardous chemotherapy drugs in low-resource settings.

1.1 Health Risks of Hazardous Drugs

In 1990, the American Society of Health-System Pharmacists, then known as the American Society of Hospital Pharmacists, defined a drug as "hazardous" based on its qualitative toxicity, including its carcinogenicity, mutagenicity, reproductive and developmental toxicity, or other acute toxicity (see Box 1). This definition was expanded by NIOSH (2004) and acknowledged that drugs with these toxic properties could pose a hazard to health care personnel. While the term "hazardous drug" can be assigned to medications used for other purposes than cancer treatment, the majority of hazardous drugs are anticancer chemotherapeutic agents. These drugs are nonselective in their action, in that they exhibit their effects in both cancerous and noncancerous cells in most organs and body tissues. Known effects in treated patients include hepatic and renal toxicity, cardiac toxicity, hematopoietic toxicity, pulmonary toxicity, immunotoxicity, ototoxicity, dermal toxicity, and particular injury to tissues with a rapid turnover rate (Barton-Burke and Wilkes 2006).

Box 1. Characteristics Defining Hazardous Chemotherapy Drugs

- Carcinogenicity
- Teratogenicity or other developmental toxicity
- Reproductive toxicity
- Organ toxicity at low doses
- Genotoxicity
- Structure and toxicity that mimics existing hazardous chemotherapy drugs

Source: Adapted from the National Institute for Occupational Safety and Health (NIOSH 2004), the Occupational Safety and Health Administration (OSHA 1999), and the American Society of Health-System Pharmacists (ASHP 1990).

In the 1970s, secondary malignancies were reported in patients who had received antineoplastic drugs for other, usually solid tumor malignancies. The most commonly seen secondary malignancies were leukemia and bladder cancer, reported after a latency period of several years (Erlichman and Moore 1996). Since that time, a number of the antineoplastic drugs, especially many of the alkylating agents, have been associated with secondary cancers in treated patients (IARC 2012). In support of these findings, numerous laboratory studies have identified these agents as rodent carcinogens and as being genotoxic in several test systems. Table 1 lists the known and probable human carcinogens among anticancer drugs in common clinical use. An additional 12 pharmaceuticals/antineoplastic agents are considered to be possible human carcinogens by the International Agency for Research on Cancer (IARC 2012).

In addition to their mutagenic and carcinogenic properties, many of the antineoplastic agents have been associated with adverse reproductive and developmental effects that have been observed both in animals and in treated male and female patients (Meirow and Schiff 2005). Currently, as shown in Table 2, more than 50 drugs present "clear evidence of risk to the human fetus," according to the U.S. Food Drug Administration. Reproductive and developmental effects similar to those observed in patients have been reported in health care workers who are exposed to antineoplastic agents at considerably lower doses than those administered to patients (Valanis et al. 1993a, 1993b; Lawson et al. 2012).

Table 1. IARC Group 1 and Group 2A Carcinogens

Group 1: Human Carcinogens	Group 2A: Probable Human Carcinogens
Arsenic trioxide	Azacitidine
Azathioprine	BCNU
Chlorambucil	CCNU
Chlornaphazine	Chlorozotocin
Cyclophosphamide	Cisplatin
Etoposide	Doxorubicin HCl
Busulfan	N-Ethyl-N-nitrosourea
Melphalan	Mechlorethamine HCl
Semustine	N-Methyl-nitrosourea
Tamoxifen	Procarbazine HCl
Thiotepa	Teniposide
Treosulfan	
MOPP[1]	
ECB[2]	

Source: Adapted from the International Agency for Research on Cancer, http://monographs.iarc.fr/ENG/Classification/index.php.

[1] Mustargen-oncovin-procarbazine-prednisone

[2] Etoposide-cisplatin-bleomycin

Table 2. Antineoplastic Agents Classified by the FDA as Pregnancy Category D or X

Drug	Pregnancy Category	Drug	Pregnancy Category
Arsenic trioxide	D	Interferon alfa-2b	X
Azathioprine	D	Irinotecan HCl	D
Bleomycin	D	Leflunomide	X
Capecitabine	D	Lomustine	D
Carboplatin	D	Mechlorethamine HCl	D
Carmustine	D	Melphalan	D
Chlorambucil	D	Mercaptopurine	D
Cisplatin	D	Methotrexate	X
Cladribine	D	Mitoxantrone HCl	D
Cyclophosphamide	D	Oxaliplatin	D
Cytarabine	D	Paclitaxel	D
Dactinomycin	D	Pipobroman	D
Daunorubicin HCl	D	Procarbazine	D
Docetaxel	D	Tamoxifen	D
Doxorubicin HCl	D	Temozolomide	D
Epirubicin	D	Teniposide	D
Etoposide	D	Thalidomide	X
Floxuridine	D	Thioguanine	D
Fludarabine	D	Thiotepa	D
Fluorouracil	D	Topotecan	D
Gemcitabine	D	Tositumomab	X
Hydroxyurea	D		
Ibritumomab tiuxetan	D	Vinblastine sulfate	D
Idarubicin	D	Vincristine sulfate	D
Ifosfamide	D	Vinorelbine tartrate	D
Imatinib mesylate	D		

Source: Adapted from the U.S. Food and Drug Administration, Center for Drug Evaluation and Research, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

Note: Category D definition: There is clear evidence of risk to the human fetus, but the benefits may outweigh the risk for pregnant women who have a serious condition that cannot be treated effectively with a safer drug. Category X definition: There is clear evidence that the medication causes abnormalities in the fetus. The risks outweigh any potential benefits for women who are (or may become) pregnant.

1.2 Evidence of Occupational Exposure

Workers may be exposed to a drug throughout its life cycle—from manufacture to transport and distribution, to use in institutional or home care settings, to waste disposal. The first evidence of occupational exposure in health care workers resulted from a study carried out by Falck et al. (1979), which indicated that nurses who prepared and administered antineoplastic drugs had higher indicators of mutagenic substances in their urine than unexposed workers. Although the health consequences of this finding are unknown, this study suggested that nursing personnel were occupationally exposed to antineoplastic drugs, many of which are mutagenic. This finding was supported by numerous subsequent studies examining urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, and other endpoints in pharmacists and nurses who handle antineoplastic drugs (Baker and Connor 1996; Sorsa and Anderson 1996; Sessink and Bos 1999; Suspiro and Prista 2011).

Surveys have also associated workplace exposure to hazardous chemotherapy drugs with acute health effects, primarily in nursing personnel. These have included hair loss, headaches, skin rashes, and allergic reactions (Valanis et al. 1993a, 1993b; Baykal, Seren, and Sokmen 2009; Constantinidis et al. 2011).

A meta-analysis of 14 studies performed from 1966 to 2004 in the United States and Europe described an association between exposure to antineoplastic drugs and adverse reproductive effects in female health care workers (Dranitsaris et al. 2005). A significant association was identified between exposure and spontaneous abortions, and a number of endpoints had elevated responses but were statistically insignificant. A recent study demonstrated a significant increase in spontaneous abortions in nurses who handled antineoplastic drugs, especially in the first trimester (Lawson et al. 2012).

It is important to note that many of these studies where an adverse effect was found occurred prior to the adoption of safe handling guidelines promoted by the Occupational Safety and Health Administration (OSHA) and professional organizations in the mid-1980s. However, these studies document the plausibility of occupational exposure intensity sufficient to cause clinically significant adverse outcomes in routinely exposed workers.

Investigations of a cancer excess in exposed workers are limited to two Danish studies. One showed a significantly increased risk of leukemia among oncology nurses identified in the Danish cancer registry for the period 1943–1987 (Skov et al. 1992). The other, by the same authors (Skov et al. 1990), found an increased risk of leukemia in physicians employed for at least six months in a department where patients were treated with antineoplastic drugs. However, the increase was not statistically significant. Despite the small number of cases observed, the biological relevance of these excess hematopoetic malignancies is underscored by the commonly observed hematopoetic second malignancies observed in treated patients (Erlichman and Moore 1996). More recently, Martin (2005) found that exposed nurses were significantly more likely to report a cancer diagnosis than unexposed nurses (OR = 3.27, p = .03).

1.3 Sources of Occupational Exposure

Exposure of health care providers to antineoplastic drugs is varied, with the typical routes of exposure being inhalation, dermal, or oral. Workers may inhale droplets, particulates, and vapors when they create aerosols or generate dust during drug preparation or while cleaning up spills. Dermal exposure may occur when workers touch contaminated surfaces during the preparation, administration, or disposal of hazardous chemotherapy drugs or patient wastes, and oral exposure may occur from hand-to-mouth contact. Other drug manipulations and work tasks also involve activities that may result in exposure through inhalation, skin contact, ingestion, or injection (NIOSH 2004, 2008).

Dermal contamination can arise from drug powders present on the outside of vials (Connor et al. 2005; Schierl et al. 2010). Thus the environment of health care personnel may be contaminated even before reconstitution of hazardous chemotherapy drugs begins. Studies have demonstrated that most work surfaces in areas where hazardous chemotherapy drugs are handled are contaminated with the drugs (NIOSH 2004). Surfaces of biological safety cabinets, counter tops, floors, equipment, and most surfaces in areas where patients are treated have been shown to be contaminated in studies from several countries around the world (Connor and McDiarmid 2006; Schierl, Bohlandt, and Nowak 2009; Connor et al. 2010; Siderov, Kirsa, and McLauchlan 2010; Yoshida et al. 2010; Sessink et al. 2011; Turci et al. 2011). Most studies involving air sampling for hazardous chemotherapy drugs have detected little to no airborne contamination with these agents (NIOSH 2004). However, this may be related to problems with the methodology used (Larson, Khaaeli, and Dillon 2003). A recent study by Mason et al. (2005) in the United Kingdom reported significant levels of several drugs in both personal and area air samples. Drug particulates can become airborne after drying on contaminated surfaces. Vaporization of antineoplastic agents has also been reported with various drugs such as BCNU, ifosfamide, thiotepa, and cyclophosphamide (Connor, Shults, and Fraser 2000; Kiffmeyer et al. 2002).

Inadvertent ingestion may be an additional route of exposure. When food or beverages are prepared, stored, or consumed in work areas, they may easily become contaminated with airborne particles of cytotoxic drugs or by contact with contaminated hands. Likewise, hands, cigarettes, cosmetics, and chewing gum can be contaminated. A potential source of exposure is direct skin contact with contaminated surfaces or during an accident or incident with spillage or leakage where a large volume of drug is released to the environment; this may result in hand-to-mouth contact.

As an indicator of internal worker exposure to hazardous chemotherapy drugs, approximately 20 studies have measured drugs in the urine of health care workers (Turci et al. 2003; NIOSH 2004; Connor and McDiarmid 2006). These are some of the same drugs used therapeutically and recovered in environmental sampling studies. Interestingly, three of the studies reported the presence of antineoplastic drugs in the urine of workers who were not actually handling the drugs, indicating secondary exposure from environmental contamination (Sessink et al. 1992; Mader et al. 1996; Pethran et al. 2003).

This evidence highlights the critical need to reduce the opportunity for those in the health care environment to be exposed to hazardous chemotherapy drugs. Efforts must be made to reduce occupational exposure to levels as low as reasonably achievable. A combination of exposure control methods can be applied to achieve this goal.

1.4 History of Safe Handling Guidelines

Since the early 1980s, when the hazards were first recognized, professional organizations of health workers and government public health agencies in the United States and other countries have published guidelines for the safe handling of hazardous chemotherapy drugs (summarized in Connor and McDiarmid 2006). Indeed, it was the ASHP Technical Assistance Bulletin of 1990 that first used the term "hazardous drug" to address other pharmaceuticals that posed a hazard to workers but were not used in cancer therapy. They proposed a scheme whereby a drug could be qualitatively characterized as "hazardous" based on its inherent toxicity. These characteristics generally relate to carcinogenicity, genotoxicity, or reproductive hazards and are listed in Box 1. Slightly more than half of the hazardous drugs that have been identified are classified as antineoplastic/cytotoxic agents, while the remainder include some hormonal agents, immune-suppressants, antiviral medications, and others (NIOSH 2012).

Although guidelines for safe handling were put in place in the mid-1980s, reports indicated that workplace contamination and worker exposure were continuing in settings where antineoplastic drugs were being prepared and administered (Connor et al. 1999; Wick et al. 2003). Therefore, the National Institute for Occupational Safety and Health (NIOSH) developed a NIOSH Alert that addressed safe handling issues for all hazardous chemotherapy drugs to renew and reinforce the existing OSHA and professional society guidelines on the problem (NIOSH 2004). Despite this guidance, studies in and outside the United States continue to document ongoing exposure (Schierl, Bohlandt, and Nowak 2009; Connor et al. 2010; Siderov, Kirsa, and McLauchlan 2010; Yoshida et al. 2010; Sessink et al. 2011; Turci et al. 2011), in part because compliance with the guidelines has been voluntary and uneven (Polovich and Clark 2012). Other safe handling guidelines have been updated by professional organizations in the last few years, including the American Society of Health-System Pharmacists (ASHP 2006) and the Oncology Nursing Society (Polovich 2011).

1.5 Control of Exposure

The basic occupational health approach to minimizing exposure to any workplace hazard uses a combination of industrial hygiene control methods that are applied in a specified order or hierarchy. This approach has achieved success across many industrial settings (Soule 1978). In most cases, the elements of this hierarchy can be applied to the health care setting (see Box 2).

Box 2. Hierarchy of Industrial Hygiene Controls

- Elimination of the hazard or substitution with a less hazardous chemical (this is not feasible in health care)
- Engineering controls (use of biological safety cabinets, isolators, or closed systems)
- Administrative controls (training and education programs; availability of safety data sheets; established work practices, policies, surveillance)
- Personal protective equipment (use of protective gloves, gowns, respiratory protection, and eye protection)

Source: Adapted from Soule 1978.

2. Safety Recommendations throughout the Life Cycle of Hazardous Drug Use

The National Institute for Occupational Safety and Health, the American Society of Health-System Pharmacists, the Oncology Nursing Society, and the International Society of Oncology Pharmacy Practitioners have current guidelines for the safe handling of hazardous chemotherapy drugs based on sound occupational health principles and professional standards of practice (NIOSH 2004; ASHP 2006; Polovich 2011; ISOPP 2007). There is considerable concurrence between the various recommendations, and also with the OSHA guidance of 1999. Highlights from the NIOSH Alert (2004) generally reflect the hierarchy of control technologies: engineering controls, administrative controls and work practices, and personal protective apparel and equipment, as shown in Box 2. Additional material may be found on the NIOSH website (http://www.cdc.gov/niosh/topics/hazdrug).

The hierarchy of hazard control technologies relies on engineering controls, such as a biological safety cabinet (BSC) or a compounding aseptic containment isolator (CACI), as the first technology applied. However, engineering solutions are often the most costly type of hazard control. In resource-limited settings where engineering controls are unaffordable or otherwise not feasible, scrupulous use of work practices that minimize aerosol and dust generation and administrative controls that limit personnel access to areas where drugs are handled can minimize exposure.

Historically, the pharmacy and patient treatment areas (clinic or ward) have been the focus of concern with respect to exposure of health care workers to hazardous chemotherapy drugs. However, Hon et al. (2011) recently demonstrated that workers in all areas of the health care facility where the drugs are present are at risk for exposure. These locations include the areas for receiving, storage, and compounding of drugs; areas through which drugs are transported; patient treatment areas; laundry services; and waste collection and storage areas (Figure 1). Therefore, all workers who are present in these areas should have appropriate hazard awareness and job task training and should take precautions to reduce exposure as much as possible.

Each of the following sections addresses safety in a specific stage of the hazardous drug (HD) life cycle. It should be noted, however, that certain safety practices are common to all of the stages. These include educating personnel on the risks; training them in work practices; training in the selection and use of personal protective equipment (PPE), especially a respirator (typically an N-95); and training in the use of hazardous drug spill kits.

Figure 1. Flow of Hazardous Drugs through the Hospital or Clinic

2.1 Receiving Hazardous Chemotherapy Drugs from the Manufacturer or Distributor

Hospitals and clinics receive medications in shipments from a manufacturer and/or distributor. These are then distributed throughout the facility for use in patient care. The transport of medications from the manufacturer can sometimes lead to broken or cracked vials or packages. It is therefore important for each employee involved in receiving the medications to inspect the packages to determine whether any are broken. Gloves should be worn when inspecting any hazardous drug package. If a hazardous drug package is damaged, the employee must assess the extent of the damage and select and put on appropriate PPE, as unprotected skin should not come into contact with the drug (see Appendix A on recommended PPE).

The following process should be used if a medication shipment has been damaged or broken:

- All personnel who receive HDs from manufacturers or distributors must be trained to wear full PPE and to use a respirator.
- Hazardous drug spill kits must be readily available in the receiving area, and receiving personnel must be trained to perform spill cleanup.
- When assessing a potentially damaged container, personnel should wear one or two pairs of gloves that have been tested and approved for use with hazardous chemotherapy drugs (ASTM 2005).
- If it is apparent that the packaging is damaged, full PPE should be worn, including double gloves, gown, eye protection, and respirator. In addition, the operator should use a spill kit to clean up and remove the damaged drug containers and packaging.

2.2 Storage of Hazardous Drugs

It is well known that hazardous drug vials are shipped from manufacturers with trace amounts of drug on the external surface (Connor et al. 2005; Schierl et al. 2010). Contamination occurs during the process of filling the vials with liquid or powder chemotherapy. Because of this, it is important for all personnel involved in the handling of HDs to wear appropriate PPE, as unprotected skin should not come into contact with the drug residue. The following recommendations should be put into place for all personnel involved in storage, retrieval, or inventorying of HDs:

- Personnel should be educated on the hazards posed by HDs and trained in the use of PPE, including a respirator for use in the event of breakage or a spill.
- Spill kits must be readily available in the HD storage area, and all personnel must be trained to perform spill cleanup.
- The storage area for HDs must have appropriate ventilation. Ideally, storage areas should have negative air pressure in relation to surrounding areas, with at least 12 air changes per hour to reduce drug residue in breathable air.
- Personnel should wear one or two pairs of gloves that have been tested and approved for use with HDs (ASTM 2005).
- Personnel should wipe each HD vial or ampoule before use, using a wiper wetted with alcohol or another appropriate solution. Never spray the HD container directly, as that transfers contamination to the air and other surfaces. The wiper should be contained and discarded after use.
- Storage areas must be cleaned at least every 30 days with detergent solution. Diluted bleach solution may also be used if the container is resistant to damage from bleach. Wipe, don't spray, HD storage bins.

2.3 Compounding Hazardous Drugs

Strict aseptic technique should be used in the compounding (preparation) of all sterile doses, whether the drug is hazardous or not. For HD compounding, it is critical to remember that the sterile dose must remain sterile but that the HD must be contained within the HD container, syringe, and IV bag and must not be allowed to contaminate the work area. See detailed technique procedures in Appendix B.

If a primary engineering control (PEC), such as a biosafety cabinet (BSC) or compounding aseptic containment isolator (CACI), is available to use in sterile compounding, it must be certified that the PEC is functional and will provide a HEPA-filtered air environment for product protection and a containment environment for personnel safety (see Appendix C). A PEC must be disinfected with 70% isopropyl alcohol prior to sterile compounding; it should be cleaned with a detergent and bleach solution, and then thoroughly rinsed with sterile water, following HD compounding.

If no PEC is available, the HD should be prepared in a quiet work space, away from heating and cooling vents and away from other personnel. Good technique is critical.

Work should be done on a disposable plastic-backed paper liner. The liner should be changed after the preparation is completed. Used liners should be disposed of as contaminated waste.

2.3.1 Compounding Technique

Proper manipulative technique to maintain the sterility of the drug and to prevent the generation of HD contaminants must be used consistently. See Appendix B for detailed recommendations. The following steps should be followed:

- Assemble all non-HD drug containers, solution containers, and supplies, including waste containment bags and disposal containers. Have an HD spill kit readily available. Select the appropriate syringes and needles to compound the dose. Syringes and IV sets with Luer-Lok™ fittings should be used for compounding and administering HD doses since they are less prone to separate than friction fittings. Care must be taken to ensure that all connections are secure.
- Select syringes that will be no more than three-quarters full when they contain the partial or full drug dose to prevent the risk of the plunger dislodging from the barrel. If more than one syringe will be needed, select them all before beginning the compounding.
- Select a needle of appropriate gauge and length for the vial and final container. If more than one needle will be needed, select them all before beginning the compounding.
- If the dose is to be placed into an IV bag, select the appropriate IV infusion set so that the IV bag can be spiked and the IV tubing primed prior to the addition of the HD.
- Wearing gloves retrieve the HD from the storage area and place with the other supplies. Remove and contain contaminated gloves for appropriate disposal.

- Wash hands before donning PPE. Full PPE including a coated gown, double HD-tested gloves, eye protection, and a respirator should be worn for compounding in the open. Put on two pairs of gloves, one under the cuff of the gown and one over the gown cuff.
- Closed-system drug-transfer devices (CSTD) or hydrophobic filter venting units should be used to reconstitute HD vials if compounding in the open to reduce the aerosols generated during the handling of needles and syringes. Only stringent aseptic technique using negative pressure in the vial should be used. See Appendix B for complete technique.
- Prepare HD drug containers by removing outer packaging and wiping off all vials or ampoules with a moist wiper to remove HD residue; discard wiper in containment bag for appropriate disposal. Do not spray alcohol or other liquids on HD ampoules or vials as the drug residue will be aerosolized and transferred to the air and other surfaces.
- Remove and contain outer gloves for appropriate disposal. Sanitize the fresh outer glove with isopropyl alcohol gel prior to compounding.
- If the dose is to be placed into an IV bag, manipulations for spiking, priming, and closing the administration tubing must all be done prior to the addition of the HD. Fasten the clamps on the IV infusion set, spike the IV bag, open the clamps, and prime the IV tubing. Fasten the tubing clamps and place a cap or connector on the end of the tubing. Be sure to keep the bag and tubing sterile.
- If using a CSTD with bag adapter, prepare the bag and tubing prior to the addition of the HD. Spike the IV bag with the bag adapter, clamp the IV tubing, and spike the IV tubing into the CSTD bag adapter. Open the clamp and prime the IV tubing. Fasten the tubing clamps and place a CSTD closed male luer connector on the end of the tubing. Be sure to keep the bag and tubing sterile.

2.3.2 Final Doses

HD doses must be in final ready-to-administer form when transported to the patient. Doses in IV bags must have the IV tubing connected and the line primed with non-HD-containing solution. Doses in syringes must be clear of air and not require any further manipulation. Final doses are placed into thick, sealable plastic bags for transport to patients. In addition to patient-specific labeling, auxiliary labels of "Hazardous Drug" should be affixed to the dose and the transport bag.

2.3.3 Containment and Disposal

Once compounding is complete and the dose has been prepared for transport, all disposable equipment and supplies must be contained and disposed of as HD-contaminated waste. Remove all PPE except for inner gloves and contain in sealable bag for disposal. (See section 2.4 for transport and section 2.6 for disposal.) Finally, remove inner gloves, contain, and dispose of as HD waste. Wash hands after completing compounding.

2.3.4 Emergency Procedures

Working in the open eliminates the protections conferred by engineering controls, which increases the risk of personnel harm if there is leakage or spillage during the compounding process. It is critical that anyone compounding HD doses in the open have immediate access to emergency supplies (such as eye wash stations and spill kits) and be trained to use them. See Appendix D for specific recommendations.

2.4 Transporting Compounded Hazardous Chemotherapy Drugs from the Pharmacy to the Patient Care Area

All HD doses should be double-bagged or placed in a sealed container for transport to the patient care area. Most organizations require the compounded sterile preparation (CSP) of a hazardous drug to be taken to the area manually, rather than by mechanical transport (such as a pneumatic tube system), which may damage the CSP and result in breakage or leakage. Use of the transport bag prevents the handler from being exposed to HDs that could have been deposited on the external surface of the finished product through the compounding process or as a result of leakage during transport. In addition, if the bag is dropped and the container breaks or leaks, there is another barrier to prevent the HD from spilling on the handler or the external environment. HD spill kits should be on the transport cart in case of an accident during transport. Only personnel trained to clean up an HD spill may transport HD doses.

2.5 Administration of Hazardous Chemotherapy Drugs

For hazardous drug administration, many of the safe handling precautions are similar no matter what route of administration is used. Certain precautions apply in all situations (ASHP 2006; OSHA 1999; Polovich, Whitford, and Olsen 2009). They require the caregiver (nurse) to:

- Wash hands before HD handling.
- Have access to a spill kit.
- Put on PPE before removing HD from the delivery container.
- Inspect the delivery container and its contents before handling.
- Wear two pairs of chemotherapy-tested gloves (NIOSH 2004).
- Wear a chemotherapy gown.
- Wear a face shield if there is a chance of the HD splashing.
- Wear a respirator if HD aerosols may be present.

- Use locking connections (e.g., Luer-Lok™) whenever possible to securely attach IV tubing, syringes, and needles.
- Avoid priming HDs into gauze pads, sinks, or trash containers.
- Perform all manipulations below eye level.
- Discard used administration sets and syringes intact to avoid contamination during disconnection.
- Dispose of equipment used in HD administration in designated waste containers.
- Remove PPE in such a way as to prevent contamination of hands and clothing.
- Dispose of used PPE. Do not hang up gowns and reuse them.
- Wash hands with soap and water immediately after removing PPE.

2.6 Handling Hazardous Drug Waste

The hospital or clinic needs to determine the process for handling the waste of hazardous drugs generated during compounding and administration or during spills, as well as wasted (bulk) products (Smith 2002). Each situation will vary, depending in part on local regulations governing waste disposal and air and water quality. It is important to determine state and local regulations to ensure compliance. Waste handling efforts should minimize the chance of contaminating the local water supply and/or soil with HDs, as they are toxic. Incineration is the preferred disposal method for most HD waste, although only special incinerators are effective in removing some of the HD residue. HD waste should never be discarded into wastewater (sink or toilet) or into a landfill.

2.7 Cleaning and Decontamination of Hazardous Chemotherapy Drug Equipment and Work Surfaces

Decontamination may be defined as cleaning or deactivating. Deactivating a hazardous substance is preferred, but no single process has been found to deactivate all currently available HDs. The use of alcohol for disinfecting a primary engineering control or other contaminated surface will not deactivate any hazardous chemotherapy drugs and may result in the spread of contamination rather than in any actual cleaning.

If available, a PEC such as a BSC or CACI should be decontaminated per manufacturer recommendations.

The safety data sheets for many HDs recommend sodium hypochlorite solution as an appropriate deactivating agent. Research has shown that strong oxidizing agents, such as sodium hypochlorite, are effective deactivators of many hazardous chemotherapy drugs.

A 2% sodium hypochlorite solution with detergent may be wiped onto contaminated surfaces, and then rinsed; this is followed by a neutralizing solution of 1% sodium thiosulfate, wiped on and

off, followed by a rinse solution of water, then alcohol. Surface contact for each solution should be at least 30 seconds. Some studies have shown good analytical results with this technique. The hazardous chemotherapy drugs may not be fully deactivated, but the wiping action followed by rinsing appears to be effective in cleaning. This technique may be used on any surface that will not be harmed by a bleach solution. All cleaning solutions, wipers, and rinsates must be contained and discarded as hazardous (Touzin et al. 2010; Zock, Soefje, and Rickabaugh 2011).

2.8 Cleanup of Hazardous Drug Spills

It is essential to have a hazardous drug spill kit immediately available in all areas where HDs are in use (see Box 3 for contents of a spill kit). These should ideally be located in places where HDs are received, stored, transported, compounded, and administered and where patient waste and drug waste are handled. HD spill kits should be placed on the transport cart when HD doses are moved throughout a facility. Each employee involved with handling HDs should be familiar with the location and use of these kits.

If a HD spill occurs, the kit should be used to clean up the spill and dispose of the contaminated waste. The process will require wearing the correct PPE, removing the HD from all of the surfaces, and cleaning the surfaces (see Appendix D).

Box 3. Suggested Contents of a Hazardous Drug Spill Kit

- Two pairs of disposable chemical-protective gloves
- Low permeability, disposable protective garment (gown or coverall, shoe covers)
- Face shield
- Respirator (N95 or better)
- Absorbent, plastic-backed sheets or spill pads
- Disposable towels
- At least two sealable, thick plastic waste disposal bags
- A disposable scoop for collecting glass fragments
- A puncture-resistant container
- Sign saying "Caution Hazardous Drug Spill"

Source: Based on information from ASHP 2006.

2.9 Safe Handling of Contaminated Bed Linen

Because HDs or the metabolites of HDs can be present in urine, blood, feces, sweat, and vomit, bed linen such as sheets, blankets, and pillowcases can be contaminated with drugs or drug products (Fransman et al. 2007). Care should be taken when handling these materials, as with other waste products. A typical recommendation is to wear protective gloves when handling contaminated linen and to place it in a labeled bag so that it can be prewashed separately and then washed with the regular laundry (ASHP 1990).

2.10 Essential Components of Medical Surveillance of Hazardous Drug Handlers

In health care institutions where some form of periodic employee health evaluation is already in place, new elements of surveillance may be added to screen HD handlers for their specific health risks (NIOSH 2013). A sample medical history questionnaire is found in Appendix E. Limited resources may preclude the implementation of a comprehensive medical surveillance program for health care workers who handle HDs. For institutions that do not have the means to develop a comprehensive surveillance program, a few key elements may serve to track employees' exposures (McDiarmid and Curbow 1992). Program elements to include in either case are as follows:

- Maintain a list of all workers who are exposed to HDs as a part of their job assignment.
- Have all HD handlers complete periodic questionnaires to track the frequency and duration of contact with these agents, their use of PPE, and any health events that are potentially related to HD exposure (see Appendix E).
- Conduct periodic observations of drug preparation and administration practices to determine the need for refresher training in work practices that reduce exposure.
- Carefully document spills, spill cleanup activities, and accidental exposure.
- Confidentially share the results of medical surveillance with the employees who handle HDs.
- Develop policies that guide employees in how to pursue surveillance through their primary care providers in settings without employee health services.

2.11 Training of Personnel Who Handle Hazardous Drugs

All health workers who may be exposed to hazardous chemotherapy drugs must undergo education and training for safe handling. Training should begin when the worker is first assigned to an area where chemotherapy agents are present and should be repeated annually. The educational content should be specific to the activities for which the worker is responsible. Appendix F outlines a suggested curriculum for nurses. Content of training for HD handlers should include some or all of the following (Polovich 2011):

- Adverse health effects from hazardous chemotherapy exposure
- Routes of occupational chemotherapy exposure
- Selection and use of personal protective equipment
- Selection and use of engineering controls as applicable
- Work practice controls that reduce exposure during chemotherapy preparation, transport, administration, and disposal, and in handling of contaminated patient waste
- Patient care issues
- Role of medical surveillance in a comprehensive program of safe handling

Following the training, knowledge should be evaluated through some form of test. In addition, performance of specific skills should be observed and evaluated using a checklist that reflects safe handling practices and the policies of the organization. An example of a checklist for safe handling of hazardous chemotherapy during administration can be found in Appendix G. Workers who are responsible for responding to spills of hazardous chemotherapy should have additional training in spill cleanup and respirator use.

3. Conclusions

The toxicity of hazardous chemotherapy drugs has been well known since their initial clinical use. Indeed, it has often been the toxic side effects of these drugs that have limited their therapeutic value. The risk-benefit equation for a cancer patient often determines these drugs' appropriate use despite acknowledged side effects. While these drugs present the same potential toxicities to exposed health care workers, that risk-benefit ratio is altered.

A body of guidance exists on how to balance the continued use of these drugs to benefit patients while ensuring the health of personnel administering them. Much of the new guidance refreshes the long-standing elements of a comprehensive safe handling program. It is important to recognize that while the risk remains, and our vigilance is still required, safer methods have been shown to limit exposure risk to workers handling these drugs while they provide life-saving therapies to their patients.

Glossary

Antineoplastic drug: A chemotherapeu¬tic agent that controls or kills cancer cells. Drugs used in the treatment of cancer are cytotoxic but are generally more damaging to dividing cells than to resting cells.

Aseptic: Free of living pathogenic organ¬isms or infected materials.

Biohazard: An infectious agent or hazard¬ous biological material that presents a risk to the health of humans or the environment. Biohazards include tissue, blood or body flu¬ids, and materials such as needles or other equipment contaminated with these infec¬tious agents or hazardous biological materi¬als. Biohazards are not chemical in nature and may be destroyed with disinfectants.

Biomarker: A biological, biochemical, or structural change that serves as an indica¬tor of potential damage to cellular compo¬nents, whole cells, tissues, or organs.

Carcinogenicity: The ability or tendency to produce cancer.

Chemotherapy drug: A chemical agent used to treat diseases. The term usually refers to a drug used to treat cancer. Similar drugs are also known as antineoplastic and cytotoxic.

Chemotherapy glove: A medical glove that has been approved by the U.S. Food and Drug Administration (FDA) for use when handling antineoplastic or chemotherapy drugs.

Chemotherapy waste: Discarded items such as gowns, gloves, masks, IV tubing, empty bags, empty drug vials, needles and syringes, and other items generated while preparing and administering antineoplastic or chemotherapy agents.

Class II biosafety cabinet (Class II BSC): A ventilated biological safety cabinet that protects personnel, product, and the work environment. A Class II biosafety cabinet has an open front with inward airflow for personnel protection, downward HEPA-filtered laminar airflow producing an ISO 5 environment for product protection, and HEPA-filtered exhausted air for environmental protection. The Class II biosafety cabinet is further defined by the method of handling contaminated air in the cabinet. Outdoor exhaust of contaminated air is preferred, as some hazardous chemotherapy drugs are not trapped by HEPA filters.

Closed-system drug-transfer device (CSTD): 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.

Compounding aseptic containment isolator (CACI): A form of isolator specifically designed for compounding pharmaceutical ingredients or preparations but also designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing

airborne concentrations of the physical size and state of the drug being compounded. Where volatile hazardous chemotherapy drugs are prepared, the exhaust air from the isolator should be appropriately removed by properly designed building ventilation.

Cytotoxic: A pharmacologic compound that is detrimental or destructive to cells within the body.

Deactivation: The process of treating a chemical agent (such as a hazardous drug) with another chemical, heat, ultraviolet light, or other agent to create a less hazardous agent.

Decontamination: Inactivation, neutraliza¬tion, or removal of toxic, noninfectious agents, usually by chemical means. Cleaning a nondisposable surface with a detergent and disposable wipers may also be an effective method of decontamination (removal) of noninfectious agents.

Engineering controls: Devices designed to eliminate or reduce worker exposures to chemical, biological, radiological, ergonomic, or physical hazards. Examples include laboratory fume hoods, glove bags, retracting sy¬ringe needles, sound-dampening materials to reduce noise levels, safety interlocks, and radiation shielding.

Genotoxicity: The ability to damage or mutate DNA. Genotoxic substances are not necessarily carcinogenic.

Hazardous drug: Any drug meeting at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low doses in humans or ani¬mals, genotoxicity, or new drugs that mimic existing hazardous chemotherapy drugs in structure or tox¬icity.

Health care worker: Any worker who is involved in the care of patients. The category includes pharmacists, pharmacy technicians, nurses (registered nurses, licensed practical nurses, nurses' aides, etc.), physicians, home health care workers, and environmental services workers (housekeeping, laundry, and waste disposal).

HEPA filter: High-efficiency particulate air filter rated 99.97% efficient in capturing 0.3-micron-diameter particles.

Horizontal laminar flow workbench (HLFW): A device (horizontal laminar flow clean bench or hood) that protects the sterile work product by supplying HEPA-filtered air to the rear of the cabinet and producing a horizontal flow across the work area and out toward the worker. This device provides no containment properties and is not appropriate for hazardous chemotherapy drugs.

Mutagenicity: The ability to increase the spon¬taneous mutation rate by causing changes in DNA.

Penetration: The movement of a chemical through zippers, stitched seams, or imperfections (e.g., pinholes) in a protective clothing material.

Permeation: The process by which a chemical dissolves in and moves through a protective clothing material on a molecular level.

Personal protective equipment (PPE): Items such as gloves, gowns, respirators, goggles, and face shields that protect indi¬vidual workers from hazardous physical or chemical exposures.

Primary engineering controls (PEC): Devices such as laminar airflow workbenches, Class II biosafety cabinets, compounding aseptic isolators, and compounding aseptic containment isolators utilized specifically for compounding sterile preparations.

Priming: Removing the air from an IV line by running IV solution from an IV bag through the tubing.

Reproductive toxicity: The ability to cause adverse effects to the male and/or female reproductive systems.

Respirator: A type of PPE that prevents harmful materials from entering the respi¬ratory system, usually by filtering hazardous agents from workplace air such as an N-95. A surgical mask does not offer respiratory protection.

Risk assessment: Characterization of po¬tentially adverse health effects from human exposure to environmental or occupational hazards. Risk assessment can be divided into five major steps: hazard identification, dose-response assessment, exposure as¬sessment, risk characterization, and risk communication.

Safety data sheet: Sheet provided by the manufacturer that summarizes the chemical prop¬erties and hazards of a specific chemical and outlines ways in which workers can protect them¬selves from exposure to the chemical.

Spike: To attach IV tubing into an IV bag by inserting the sharp spike of the set into the administration port of the IV bag.

Standard precautions (formerly univer¬sal precautions): The practice in health care of treating all patients as if they were infected with HIV or similar diseases by using barriers to avoid known means of transmitting infectious agents. These barriers can include nonporous gloves, goggles, and face shields. Careful handling and disposal of sharps or the use of needleless systems are also important.

Teratogenicity: The ability to produce fetal malformation.

Appendix A

Recommendations for Use of Personal Protective Equipment when Handling Hazardous Chemotherapy Drugs

The essential elements of personal protective equipment for workers handling hazardous drugs include gloves, gowns, respiratory protection, and eye and face protection.

Gloves

Surfaces in areas where hazardous chemotherapy drugs are present may be contaminated with these drugs. Not all gloves offer adequate protection from dermal exposure to hazardous chemotherapy drugs: some gloves may permit rapid permeation of the drugs. For example, polyvinyl chloride exam gloves offer little protection against drug exposure. Although thicker gloves may offer better protection, glove thickness does not always indicate the level of protection and may make work activities more difficult.

Currently, guidelines are available for testing "chemotherapy gloves," and information may be available from the glove manufacturers (ASTM 2005).

Gloving materials such as latex and nitrile have been tested against permeation of chemotherapy. However, current issues with sensitivity to latex in workers and patients have made latex less desirable in clinical use.

Follow these work practices when using gloves:

- Inspect gloves for defects before use; do not use gloves with thin spots or pinholes. Change gloves on a regular basis. Changing recommendations vary from 30 to 60 minutes depending on the effectiveness of the glove and the permeation properties of the gloving material in relation to the specific drug. Whenever gloves are damaged or contact with a drug is known or suspected, carefully remove and dispose of the gloves properly.
- Use powder-free gloves, since powder can contaminate the work area and can absorb and retain hazardous drugs. Skin contact with contaminated powder may increase the risk of drug absorption.
- Wear two pairs of gloves when compounding, administering, and disposing of hazardous drugs. Wear the inner glove under the gown cuff and the outer glove over the cuff. Place gloves with long cuffs over the cuff of the gown to protect the wrist and forearm.
- When compounding sterile preparations, sanitize gloves with sterile 70% alcohol spray or gel and allow them to dry before handling hazardous chemotherapy drugs. To sanitize gloves during compounding, use alcohol on a towel to wipe gloves (spraying contaminated gloves may transfer drug into the air or onto other surfaces). Contain and discard any contaminated toweling.

- When removing double gloves, remove outer gloves first. Touch dirty surfaces to other surfaces; never touch the skin with contaminated gloves. Remove one outer glove by pinching the wrist of the glove with the gloved fingers of the other hand. Roll the glove down the hand to the fingers so that the inside of the glove is outside. Make a ball of that glove in the gloved hand. Using the hand wearing the inner glove, place two fingers under the wrist of the second outer glove (inner glove is less contaminated and should not touch the surface of the outer glove). Roll that glove off the hand and over the balled glove. The outer pair of gloves is now inside out and the first glove contained inside the second. Use the inner gloves to remove and contain the gown, then remove the inner gloves by touching glove to glove and skin to skin so that contaminated surfaces do not touch uncontaminated surfaces.
- Contain contaminated gloves in disposable bags and dispose of appropriately as waste.
- Wash hands thoroughly with soap and water both before donning and after removing gloves.

Gowns

Gowns made of appropriate material protect the worker from spills and splashes of hazardous chemotherapy drugs, drug waste, and bodily waste. Gowns should not have seams or closures that could allow drugs to pass through. Gowns should not open in the front. They should have long sleeves with tight-fitting cuffs. Disposable gowns made of polyethylene-coated polypropylene or other laminate materials offer better protection than those of uncoated materials. Cloth laboratory coats, surgical scrubs, or other absorbent materials permit the permeation of hazardous chemotherapy drugs and can hold spilled drugs against the skin and increase exposure.

Follow these work practices when wearing gowns:

- Wear gowns whenever there is a possibility of splash or spill, as in compounding or administration of hazardous chemotherapy drugs and in spill cleanup.
- Do not wear gowns outside the compounding or administration area. This is to avoid spreading drug contamination from the outside of the gown to other areas and possibly exposing unprotected workers.
- If no permeation information is available for the gowns in use, change them every two to three hours or immediately after a spill or splash.
- Dispose of gowns after each use. Gowns become contaminated during use. Reusing gowns increases the likelihood of exposure to hazardous chemotherapy drugs by transferring contamination from the gown surface to other surfaces, including skin.

Respiratory Protection

For most activities requiring respiratory protection, a NIOSH-certified N95 or more protective respirator is sufficient to protect against airborne particles. These respirators offer no protection against gases and vapors and little protection against direct liquid splashes. A surgical N95 respirator provides the respiratory protection of an N95 respirator and the splash protection provided by a surgical mask. Surgical masks alone do not provide respiratory protection from chemotherapy drug exposure and should not be used when compounding or administering hazardous chemotherapy drugs.

Eye and Face Protection

Proper eye and face protection is needed whenever hazardous drugs may splash in the eyes, since many hazardous drugs are irritating to eyes and mucous membranes and may be absorbed by the eyes.

Follow these work practices when using eye and face protection:

- Use eye and face protection when compounding a drug outside a primary engineering control such as a biosafety cabinet or compounding isolator (e.g., in the operating room), or when working at or above eye level, cleaning a primary engineering control, or cleaning a spill.
- Use face shields in combination with goggles to provide a full range of protection against splashes to the face and eyes. Face shields alone do not provide full eye and face protection.
- Do not use eyeglasses or safety glasses with side shields, as they do not adequately protect the eyes from splashes. A full face piece respirator also provides eye and face protection.

Appendix B

Stringent Techniques for Compounding Sterile HD Doses

Compounding sterile doses of hazardous drugs (HDs) requires precautions to ensure that sterility is not compromised by adding any non-sterile substance into the drug vial and that no drug residue as aerosol or spill is allowed out of the drug vial. Ampoules must be handled carefully to avoid either form of contamination and to prevent cuts or scrapes resulting from the sharp edges of the open ampoule. These procedures assume a working knowledge of standard aseptic technique and are specific to the stringent techniques used to compound HDs.

General Instructions

- Compound in a suitable primary engineering control (PEC) if available, or in an appropriately prepared open compounding site (see section 2.3).
- Wash hands before donning personal protective equipment (PPE).
- Wear appropriate PPE for compounding in a PEC or in the open (outside a containment cabinet). Full PPE including a coated gown, double HD-tested gloves, eye protection, and an N-95 respirator plus face shield should be worn for compounding in the open.
- Sanitize gloves routinely by wiping with a sterile cloth saturated with alcohol. Do not spray alcohol on contaminated gloves as that will transfer contamination to the environment and other surfaces.
- Wipe off all vials or ampoules of HD with a moist wiper to remove HD residue. Discard wiper in containment bag for appropriate disposal.
- Select syringes that will be no more than three-quarters full when containing the partial or full drug dose.
- Select needles of appropriate gauge and length for the vial and final container.
- If the syringe is the final delivery device, select a locking cap for the syringe.
- If the dose is to be placed into another container, such as an IV bag or bottle, select and prepare the container for injection of the HD dose by removing any outer wrap and spiking the bag/bottle with the appropriate IV set. Prime the IV set with IV solution from the bag/bottle before adding HD to the final container. Swab the injection port with a sterile alcohol wipe and allow the alcohol to dry.
- The use of a closed-system drug-transfer device (CSTD) or hydrophobic filter venting unit may improve containment of HD during compounding only if personnel are fully trained to use such devices.

Hint: Adding colored dye (such as food coloring) to water for injection vials provides a good training and practice tool for mastery of HD technique.

Vials

Unpunctured vials may have positive or negative pressure in relation to the work area. In making the first puncture, always anticipate positive pressure to avoid the contents of the vial "spitting" HD-contaminated drug or air as an aerosol.

- To reconstitute a powdered drug in a vial, calculate the amount of diluent needed to achieve the desired concentration.
- Remove plastic protector caps from the HD vial and the diluent vial.
- Using a sterile swab of 70% isopropyl alcohol, swab each vial three times in the same direction, using a new swab for each vial. Allow alcohol to dry.
- Using standard aseptic technique, draw up the exact amount of diluent in a syringe large enough to be no more than three-quarters full when containing the entire dose, with attached needle.
- With the HD vial on the work surface, position the syringe and needle so that the bevel of the needle is facing up and away from you. Insert the needle at a 45-degree angle into the closure of the vial until the bevel is half covered.
- Bring the needle and syringe perpendicular to the vial closure and insert the needle through the closure into the vial. Be sure the needle is in the vial and no part of this critical site is exposed during reconstitution.

- Draw back on the plunger of the syringe and aspirate air out of the vial into the syringe, creating a negative pressure in the vial. Do not push on the plunger.

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- Allow the diluent in the syringe to move into the vial (to correct the negative pressure) without pushing on the plunger. If you must push on the plunger, do so slowly and carefully, exchanging small amounts of liquid and air.
- Repeat these steps until all the diluent is in the vial and the air is in the syringe.
- With the needle fully in the vial, hold the syringe and vial firmly and gently swirl or rotate the drug vial to ensure that all the drug powder is in solution.

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- The syringe should now contain all the air from the vial and the pressure is even.

To remove the needle and syringe from the vial:

- move the needle to the top of the vial into the air space above any drug solution. Draw back on the plunger of the syringe and aspirate enough air out of the vial into the syringe to create a slight negative pressure in the vial (about 1–2 milliliters; more air will cause the syringe plunger to be drawn back into the syringe barrel by the negative pressure in the vial). This also clears the needle of drug solution.

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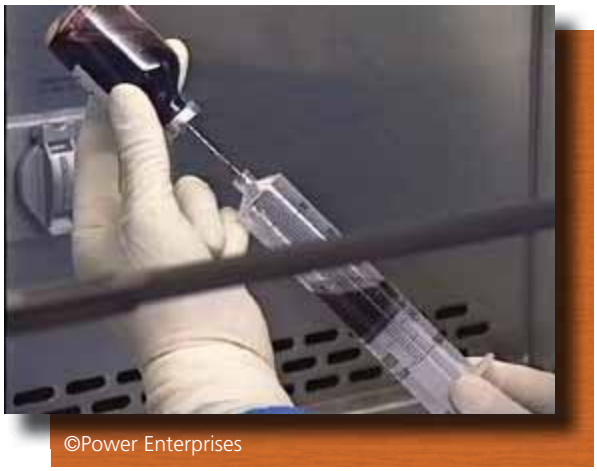
To remove the syringe and needle from the vial:

- Hold the syringe and plunger firmly with one hand and the drug vial in the other hand and carefully separate the syringe and needle from the HD vial; this leaves the HD vial at a slight negative pressure. Discard the syringe and needle into an appropriate sharps waste container.

To remove the dose from the vial without removing the needle and syringe:

- If the entire vial is to be used immediately, and if the entire dose will fit into the one syringe, keep the needle fully in the vial, invert the vial, and draw back on the plunger of the syringe to aspirate HD solution into the syringe and create negative pressure in the vial. This will cause the air in the syringe to flow into the vial but will not pressurize the HD vial. (The process of pushing air into the HD vial creates pressure in the vial and may cause the HD solution to leak from the vial septum around the needle—especially with the vial inverted and the solution on the septum.)



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- Continue to draw back on the syringe plunger, exchanging fluid for air until the desired amount of the contents of the vial is in the syringe. Draw back on the plunger to bring air into the syringe and swirl the syringe to bring all air bubbles to the top of the syringe. Holding the syringe at a 90-degree angle, carefully inject all excess air back into the vial. The syringe should be no more than three-quarters full with the desired vial contents and no air bubbles should be in the HD solution. This ensures correct measurement of the HD in the syringe. Repeat if needed to be sure that all air bubbles are out of the syringe.
- Once the dose is contained in the syringe, hold the syringe and plunger firmly and place the HD vial upright on the work surface. The needle should still be fully into the vial. Partially withdraw the syringe from the vial until only a portion of the needle is still in the vial. Holding the vial and the syringe and plunger, draw back on the plunger of the syringe to aspirate a small amount of air out of the vial into the syringe just to the shoulders of the hub of the syringe. This will clear the needle of any drug. Do not aspirate additional air into the HD solution as this will require removing the air bubble from the syringe. (This will require repeating the steps above to remove excess air from the syringe.)


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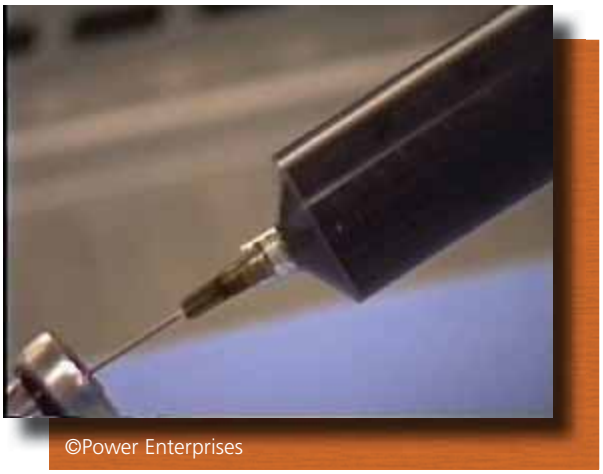
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- Fully withdraw the syringe and needle from the vial. If the contents of the syringe must be checked by another staff member, carefully recap the needle using a one-handed technique (see Box B.1).

Box B.1 The One-Handed Needle Recapping Method

Recapping a needle in clinical use represents an infectious hazard. While a needle used in HD compounding does not represent an infectious risk, there is a risk of stabbing, scratching, or injecting the skin with drug solution. The U.S. Food and Drug Administration recommends this method of needle recapping:

Step 1: Place the cap on a flat surface like the table or counter with something firm to "push" the needle cap against.

Step 2: Holding the syringe with the needle attached in one hand, slip the needle into the cap without using the other hand.

Step 3: Push the capped needle against a firm object to "seat" the cap onto the needle firmly using only one hand.

Source: "What to Do If You Can't Find a Sharps Disposal Container," FDA website, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/Sharps/ucm263259.htm.

- If the dose is to be delivered in the syringe, carefully recap the needle using the one-handed technique and prepare a locking syringe cap. Holding the syringe upright, carefully remove the needle and replace it with the locking cap.

- If the dose is to be immediately injected into a secondary container with no check, swab the container port and inject. If the container has positive pressure in relation to the work area, draw back on the syringe plunger after puncturing the container port, and then carefully push on the plunger to empty the syringe. Clear the needle by drawing air from the IV bag/bottle into the syringe before withdrawing the needle and syringe from the final container. Discard the syringe and needle into an appropriate sharps waste container.

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- Swab the container port to remove any HD residue and cap the port with an appropriate seal. Remove gloves and replace with clean gloves. Wipe down the outside of the container to remove any HD residue generated during compounding that might have settled on the container or been transferred from the gloves worn during compounding before labeling the final container.

To remove a dose of an already reconstituted drug from vial:

- When removing a dose from a reconstituted drug vial, select a new syringe that will be no more than three-quarters full when containing the HD dose. Attach the appropriate needle and remove the needle cap. As this is a second puncture into a vial, use a needle one gauge smaller than the original puncture, if possible, to avoid stressing the vial closure and causing leakage.

- Draw a volume of air into the syringe just slightly less than the volume of HD solution you will be withdrawing.

- Examine the closure of the vial to identify the previous puncture. Be sure the closure has sealed around the existing puncture. With the reconstituted HD vial upright on the surface, position the syringe and needle so that the bevel of the needle is facing up and away from you. Insert the needle at a 45-degree angle into a new area of the HD vial closure until the bevel is half covered.

- Repeat previous steps to withdraw HD. Note: As the vial was at negative pressure and the amount of air withdrawn into the syringe was less than the volume of solution withdrawn, the vial should be under negative pressure. Maintain negative pressure when removing the needle and syringe from the vial, as described above.

To use a vial that contains a liquid HD:

- To draw a dose from a vial containing a liquid HD, consider that the unpunctured vial may be at positive, negative, or neutral pressure in relation to the workplace. Given this uncertainty, it is prudent to draw a volume of air into the syringe just slightly less than the volume of HD solution you will be withdrawing. Create and then maintain negative pressure in the vial, as described above.

Once you have mastered these tasks for compounding HD doses from vials, any combination of them may be used to produce a dose from a partial vial, a dose from multiple vials, multiple doses from a vial, multiple doses from multiple vials, etc. Larger vials and syringes present a potential difficulty. Practice with water for injection prior to compounding HDs.

Ampoules

Ampoules are difficult to manipulate, as once opened there is no barrier to the sterile liquid. Precautions must be taken to avoid microbial contamination as well as HD escaping into the environment. Working with ampoules in the open (outside a containment cabinet) is a particular risk for respiratory and eye contamination. An N95 respirator plus face shield therefore should be worn for compounding in the open.

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- Select a filter needle for use with an ampoule. The filter is used to draw HD from the ampoule, then removed, and a new needle is used to inject the HD into the final container.
- Place the ampoule(s) of drug on the work surface.
- Make sure all liquid has been cleared from the neck of the ampoule. If not, tap it gently on the work surface to clear the neck.

- Swab the neck of the ampoule with a sterile swab of 70% isopropyl alcohol and allow the alcohol to dry.

- Attach the filter needle to the appropriate syringe and loosen but retain the cover.
- As with all HDs, the syringe should be no more than three-quarters full when containing the HD dose.
- Select a new swab and place it around the neck of the ampoule. Place the hands so that the thumb and index finger of the dominant hand are on the top of the ampoule, above the neck, and the thumb and index finger of the other hand are below the neck of the ampoule. Face the ampoule away from open space or workers.
- Holding the ampoule at a slight angle, grasp the top of the ampoule and break it off with a sharp snapping motion, pulling up and away from the ampoule. The swab should contain the top of the ampoule and any HD that splashed out during opening. Contain and discard the swab and top of the ampoule.

- Tilt the ampoule slightly and insert the tip of the filter needle, being careful to touch only the sterile insides of the ampoule. The short filter needle will probably not reach the bottom of the ampoule so the ampoule must be carefully tilted to bring the HD solution to the needle.

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- Pull back on the syringe plunger to withdraw the desired volume of HD solution.
- Carefully recap the filter needle to remove it.
- Place a new needle on the syringe if the HD dose is to be injected into a secondary container.
- Replace the filter needle with a cap if the dose is to be delivered in the syringe.
- Contain the ampoule in a sealable container and discard as either empty (if it is empty) or as a partial dose in the appropriate HD waste stream.

Appendix C

Ventilated Cabinets and Other Engineering Controls

Engineering controls are devices designed to physically eliminate or reduce worker exposures to chemical, biological, radiological, or other hazards. Ventilated cabinets are a type of ventilation or engineering control designed for the purpose of worker protection (NIOSH 2004). In the context of handling hazardous chemotherapy drugs, the ventilated engineering control must protect the worker from exposure to drug particles, as powder or liquid aerosols, and drug vapors. The control should also provide some protection against spills. As these drugs are also environmental hazards, an effective engineering control also provides protection to the environment by physically containing the hazard through the use of high-efficiency particulate air (HEPA) filters or an exhaust system that removes exhaust air generated during the compounding process, shielding the worker and work area from contact. As a number of hazardous drugs routinely used in patient care may not be trapped by a HEPA filter, external exhaust through a dedicated exhaust ventilation system is preferable (NIOSH 2004; USP 2011).

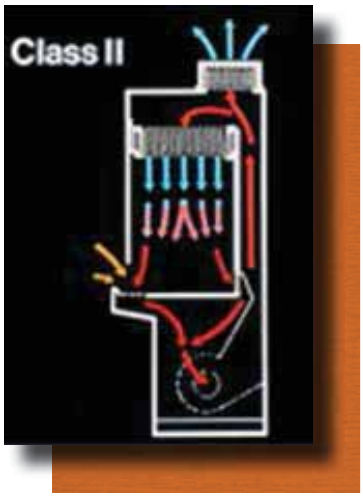
Engineering controls used in compounding sterile products must also provide product protection to ensure that the product remains sterile. This is generally achieved by using HEPA filters and air flow to create a "clean air" environment in which to expose sterile surfaces, such as needles, and protect direct pathways to sterile powders and liquids.

Most guidelines for the safe handling of hazardous chemotherapy drugs advocate a Class II biological safety cabinet (BSC) as the primary engineering control. A Class II BSC is a ventilated cabinet that protects personnel, product, and the work environment. It has an open front with inward airflow for personnel protection; downward HEPA-filtered laminar airflow producing a clean-air, low-particulate environment to reduce the chance of microbiological contamination for product protection; and HEPA-filtered exhausted air for environmental protection. The Class II BSC is further defined by the fact that contaminated air is handled in the cabinet. Outdoor exhaust of contaminated air is preferred, as some hazardous chemotherapy drugs are not trapped by HEPA filters (NSF/ANSI 2007). Design and performance requirements for biosafety cabinets are well established for biological and infectious agents, both nationally and internationally (WHO 2004; NSF/ANSI 2007).

One concern about the Class II BSC is that it has a partially open front and is dependent on an inward airflow barrier to contain drug contaminants in the cabinet. Poor technique or drafts within a work area may compromise this containment. Studies have shown hazardous chemotherapy drug residue on the floor in front of this type of cabinet.

Class II biological safety cabinet

Photo courtesy of NuAire, Inc.



Airflow of Class II BSC

Photo courtesy of NuAire, Inc.

Due to concerns about drug residue escaping the Class II BSC, alternative ventilated engineering controls have become available. One such alternative is a type of barrier isolator or glove box, a device that provides a physical barrier between a worker and a work process. The internal work space is accessed through transfer ports or glove ports. Unlike the BSC, isolators have few design requirements and even fewer performance criteria, as reflected in the variety of types of isolators on the U.S. market. The U.S. Pharmacopeial Convention, a pharmacy regulatory body, has adopted stringent criteria for isolators used to compound sterile products (compounding aseptic isolators, CAI) and those for compounding hazardous sterile products (compounding aseptic containment isolators, CACI) (USP 2011).

Compounding aseptic containment isolator (CACI)

Photo courtesy of NuAire, Inc.

In that document, a CACI is a form of ventilated isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations. Air exchange from the isolator with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where volatile hazardous drugs are prepared, the exhaust air from the isolator should be appropriately removed by properly designed building ventilation (USP 2011).

An isolator that meets the USP chapter 797 criteria for a CACI may be used to compound sterile hazardous chemotherapy drugs, as it provides worker, product, and environmental protection. The Class II BSC and the CACI must be used with personal protective equipment (PPE) and stringent work practices to ensure sufficient reduction of the risk of worker exposure to HD.

An additional engineering control is the closed-system drug-transfer device (CSTD). Available through a number of manufacturers, the CSTD provides a barrier that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system. At least one CSTD has been shown to reduce surface contamination and worker exposure in clinical use (NIOSH 2004). NIOSH, the American Society of Health-System Pharmacists, and the U.S. Pharmacopeial Convention recommend using a CSTD (NIOSH 2004; ASHP 2006; USP 2011).

Appendix D

Emergency Procedures for Personnel Contamination with Hazardous Chemotherapy Drugs and for Hazardous Drug Spills

Personnel Contamination

Direct contact with hazardous drug (HD) powder or liquid is a serious source of exposure. Many HDs are absorbed through the skin; in addition, HDs may be caustic to the eyes, may damage and penetrate mucous membranes, and may present respiratory hazards. Workers who have direct skin or eye contact with HDs require immediate treatment.

Procedures must be in place to address personnel contamination, and protocols for medical attention must be developed before any direct contact occurs. All personnel in HD areas must know how to treat direct contact with HDs and know the procedure for obtaining medical attention.

All areas where HDs are handled (including areas for receiving, storage, transport, compounding, administration, patient care, or spill and waste management) must have running water or emergency kits readily available. Supplies for emergency treatment (e.g., soap, eyewash, sterile saline for irrigation) should be immediately located in any area where HDs are handled.

Direct skin or eye contact, or contamination of protective equipment or clothing, should be treated through the following steps (adapted from Polovich 2011):

- Immediately remove the contaminated gloves or gown and clothes.
- Immediately cleanse the affected skin with soap and water.
- Perform decontamination based on the safety data sheet for the agent of exposure.
- In the case of eye exposure, flood the affected eye at an eyewash fountain or with water or isotonic eyewash designated for that purpose for at least 15 minutes.
- Obtain medical attention. Protocols for emergency procedures should be maintained at the designated sites for such medical care. Medical attention should also be sought for inhalation of HDs in powder form.
- Medical personnel should perform a physical examination for acute findings at the site of exposure (e.g., skin or inhalation). Also focus on target organs of the drug or drugs involved.
- Obtain blood for baseline counts and archiving (spin and freeze) so that there is a value to compare to in case of future changes. In terms of laboratory results, a specimen collected immediately after an exposure is almost as good as a pre-exposure specimen.

- Appropriate follow-up times can be determined based on the drug half-life and, for example, expected nadir of blood counts.
- Document the exposure in the employee's medical record.

Spills

HD spill kits should be assembled or purchased and should contain sufficient supplies to clean up at least 1,000 milliliters of volume. HD spill kits must include all the PPE needed to protect a worker when handling liquid or powdered spills in an open environment. An approved respirator and goggles and/or face shield must be included (see Box 3, Suggested Contents of a Hazardous Drug Spill Kit). Clearly labeled spill kits should be kept in or near all HD handling areas.

The spill area should be identified with a warning sign to limit access to the area. Incident reports should be filed to document the spill and persons exposed.

Appendix E

Annual Medical Survey for Hazardous Drug Handlers

A. Medical history

1. In the course of the past year, have you had any changes in your general health?

_____ YES _____ NO

If yes, please describe: _____

_____

2. In the course of the past year, have you had any of the following symptoms?

Symptom	No	Yes	Have you noticed that these symptoms occur in relation to your work? (e.g., either during the workday or immediately after)
Bruising			
Dizziness			
Facial flushing			
Fever			
Gastrointestinal complaints			
Hair loss			
Headache			
Nausea			
Nosebleed			
Respiratory symptoms			
Skin rash			
Sore throat			
Vomiting			
Wheezing			
Other (specify):			

Unintentional weight loss? _____ YES _____ NO If yes, how many pounds? _____

3. In the course of the past year, or since you last completed this questionnaire, have you had any of the following reproductive events listed below?

a) Have you or your partner ever had a problem conceiving a child? _____ YES _____ NO

b) Have you or your partner consulted a physician for a fertility or other reproductive problem? _____ YES _____ NO

If yes, who consulted the physician: _____ self _____ partner _____ self and partner

If yes, please state the diagnosis that was made: _____

c) In the past year, have you or your partner conceived a child resulting in a miscarriage, stillbirth, or birth defect? _____ YES _____ NO

If yes to question (c), please specify the type of outcome:

_____ miscarriage _____ stillbirth _____ birth defect

If the outcome was a birth defect, please specify the type or describe: _____

_____

d) What is the occupation of your spouse or partner? _____

e) For women only: In the past year, have you had any menstrual irregularities? _____ YES_____ NO

If yes, please specify the type of menstrual irregularity: _____

If yes, how many episodes of this irregularity did you have (in the past year)?_____

B. Work History

1. How many hours a week do you usually work with hazardous drugs (either handling, or in the area where they are being handled)? _____

2. Has this schedule changed over the past year? _____ YES _____ NO If yes, how has it changed? _____

   _____

   In the course of the past year, have you been around an antineoplastic drug spill? _____ YES _____ NO

   If yes, please give approximate date or dates (if this occurred more than once) _____

   If yes, approximately how large was the spill? _____ Less than 5 ml _____ More than 5 ml

   If yes, did you clean it up? _____ YES _____ NO

   If yes, what protective clothing were you wearing when spill occurred? _____
   ____

   _____

3. In the course of the past year, have you accidentally ingested, breathed in, or had skin contact with an antineoplastic drug or solution? _____ YES _____ NO

   If yes, how often? _____

Source: M. Polovich, ed., Safe Handling of Hazardous Drugs (Pittsburgh: Oncology Nursing Society, 2011). Reprinted by permission. Based on information from McDiarmid and Curbow 1992.

Appendix F
Hazardous Drug Administration Practicum for Nurses

Objective	Content	Teaching/Learning Strategies
Section 1: Review of Safe Handling Practices		
Recall the properties and health risks of workplace exposure to hazardous chemotherapy drugs.	Characteristics of hazardous chemotherapy drugs: • Carcinogenicity • Reproductive toxicity • Teratogenicity or developmental toxicity • Infertility • Organ toxicity at low doses • Genotoxicity • Drugs similar in structure or toxicity	Discuss clinical scenarios regarding potential exposure • Case study: Nurse attempting to conceive • Case study: Experienced nurse who chooses not to wear PPE • Case study: Explain to patient and family why you are wearing PPE Learner will interview nursing staff on their PPE practices in light of current evidence and will evaluate feedback in light of recommended practices. In advance of clinical experience, learner will download and review: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Health Care Settings http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf Materials: • NIOSH Alert • Case studies
Outline potential routes of exposure in the clinical setting.	Potential routes of exposure include: • Skin or mucous membrane exposure • Needlesticks or sharps • Inhalation of aerosols, dust, or droplets • Ingestion Common exposure scenarios: • Manipulation of vials • Opening ampoules • Expelling air from syringes • Drug administration by all routes • Spiking IV (intravenous) bags and changing IV tubing • Leakage of tubing or IV bags or syringes • Contamination of objects in the environment • Handling body fluids of patient who has received chemotherapy • Cleaning up spills	Discussion and question and answers with instructor Review clinical setting for possible exposure scenarios by walking through and observing administration of chemotherapy Learner will journal about practices observed and identify potential areas for improvement

continued

Hazardous Drug Administration Practicum for Nurses (continued)

Demonstrate safe handling, administration, and disposal of hazardous chemotherapy drugs in accordance with recommended best practices.	• Overview of appropriate drug storage, transportation, handling, and disposal procedures • NIOSH Alert regarding safe handling and disposal of hazardous chemotherapy drugs • Review and practice safe handling techniques using personal protective equipment, including gloves, gowns, respirator, eye and face protection • Rationale for PPE use • Review work practice controls to minimize environmental contamination, such as not spiking at the bedside, working below eye level, use of PPE, closed-system devices if available, using gauze under syringe at injection ports, using Luer-Lok™ connections when possible, safe priming of IV tubing, washing exposed surfaces with detergent and water, and proper disposal technique • Standard precautions, including double gloving and disposable gowns, when handling excreta of patients who have received hazardous chemotherapy drugs in previous 48 hours • Use of face protection when splashing is possible • Use of leakproof pads for patients at home or inpatient • Linen handling procedures • Review spill management procedures according to best practice	Clinical observation with patients receiving chemotherapy Under supervision of instructor, perform: • Return demonstration of appropriate PPE use while administering hazardous chemotherapy drugs • Return demonstration of work practice controls to minimize environmental contamination • Return demonstration of proper disposal technique utilizing hazardous waste receptacles • Instruct patient and family on safe handling practices, including hand-washing, PPE, safety of children and pets, management of linens and contaminated objects • Locate spill kit and review contents Materials: • NIOSH Alert pamphlet • ONS Guidelines, Appendix 5, Cancer Chemotherapy Administration Competency Record (Polovich, Whitford, and Olson 2009, p. 356) • ONS Guidelines, Appendix 3, Safe Management of Chemotherapy in the Home (Polovich, Whitford, and Olson 2009, pp. 353–54) • Spill kit matching game to identify use of each component In advance of clinical experience, learner will download and review: CDC Workplace Solutions: Personal Protective Equipment for Health Care Workers Who Work with Hazardous Drugs http://www.cdc.gov/niosh/docs/wp-solutions/2009-106/pdfs/2009-106.pdf
Explain the concept of medical surveillance as a component of a safe handling program.	Definition of medical surveillance: • Comprehensive program to minimize workplace exposure • Engineering controls • Work practices • PPE • Elements of a medical surveillance program • Health surveys • Laboratory work • Physical exam • Rationale for follow-ups	Discussion with preceptor Visit to occupational health for medical surveillance program enrollment In advance of clinical experience, learner will download and review: CDC Workplace Solutions: Medical Surveillance for Health Care Workers Exposed to Hazardous Drugs, http://www.cdc.gov/niosh/docs/wp-solutions/2013-103/pdfs/2013-103.pdf

Source: M. Polovich, ed., Safe Handling of Hazardous Drugs (Pittsburgh: Oncology Nursing Society, 2011). Reprinted by permission

Appendix G

Checklist for Safe Handling of Hazardous Drugs during Administration

Name:_____ Date of Review and Exam: _____

	Yes	No	Initials
Prior to Administration			
1. Gather equipment required for drug administration.			
2. Select appropriate gloves for hazardous drug administration.			
3. Select appropriate gown for hazardous drug administration.			
4. Identify situations when face shield/eye protection is required.			
5. Locate spill kit and mask.			
6. Obtain hazardous waste container.			
7. Receive drug(s) from pharmacy in sealed container.			
Administration			
1. Wash hands and don gown and gloves before opening drug delivery bag.			
2. Visually inspect the contents of the delivery bag.			
3. Don face shield, as indicated.			
4. Select IV equipment with locking connections.			
5. For IV infusions:			
• Place plastic-backed absorbent pad to protect patient from droplets.			
• Remove cap from IV tubing and connect to patient delivery site.			
• Tighten locking connections.			
• When complete, discontinue IV bag/bottle/tubing intact and re-cap patient delivery site.			
6. For IV push medications:			
• Wrap gauze around connection to catch drug droplets.			
• Tighten locking connection.			
• When complete, remove syringe from needleless connection.			
• Discard syringe and waste in a puncture-proof/leakproof container.			
7. For IM/SQ injections:			
• Attach needle to syringe.			
• Tighten locking connection.			
• When complete, do not re-cap needle.			
• Discard syringe-needle unit in puncture-proof/leakproof container.			
8. For oral drugs:			
• Don gloves.			
• Open unit dose package and place into medicine cup (avoid touching drug or inside of package).			

continued

Checklist for Safe Handling of Hazardous Drugs during Administration (continued)

Post-Administration			
1. Don gown, gloves, and face shield, if indicated.			
2. Seal contact material in plastic bag for transport to hazardous waste container.			
3. Place sealed plastic bag in hazardous waste container.			
4. Remove PPE properly, seal it in a plastic bag, and dispose of it in the hazardous waste container.			
5. Close lid on waste container.			
6. Wash hands thoroughly after removal and disposal of PPE.			
7. Decontaminate equipment appropriately in the area.			

Source: M. Polovich, ed., Safe Handling of Hazardous Drugs (Pittsburgh: Oncology Nursing Society, 2011).Reprinted by permission
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Appendix H
Resources

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