

Section VI

*(previously Section V of Oregon OSHA's Technical Manual)*

**HEALTH CARE FACILITIES**

**CHAPTER 1:** HOSPITAL INVESTIGATIONS:  
HEALTH HYAZARDS

**CHAPTER 2:** [CONTROLLING OCCUPATIONAL  
EXPOSURE TO HAZARDOUS  
DRUGS](#)

**CHAPTER 3:** [RESERVED]

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## SECTION VI: CHAPTER 2

# CONTROLLING OCCUPATIONAL EXPOSURE TO HAZARDOUS DRUGS

### Chapter Revision Information:

- *This chapter was previously identified as Section V, Chapter 3 in Oregon OSHA's circa 1996 **Technical Manual**. The section number was modified from Section V to Section VI in March 2014 to provide uniformity with federal OSHA's Technical Manual (OTM). The chapter number was modified from Chapter 3 to Chapter 2.*
- *In March 2014, the chapter's multilevel listing format was modified from an alphanumeric system to a roman numeral system.*
- *In March 2014, all references to "Material Safety Data Sheets (MSDS)" were changed to "Safety Data Sheets (SDS)."*
- *In March 2014, all references to "OSHA 200 Log" were changed to "OSHA 300 Log."*
- *In March 2014, a reference to 29 CFR 1910.133 was replaced with OAR 437-002-0134.*
- *In March 2014, a reference to "29 CFR 1910.20(Employee Records)" was replaced with "29 CFR 1910.1020 (Access to Employee Exposure and Medical Records)."*

**SECTION VI: CHAPTER 2**

**CONTROLLING OCCUPATIONAL EXPOSURE TO  
HAZARDOUS DRUGS**

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## **I. Introduction**

In response to numerous inquiries,<sup>1</sup> OSHA published guidelines for the management of cytotoxic (antineoplastic) drugs in the work place in 1986.<sup>106</sup> At that time, surveys indicated little standardization in the use of engineering controls and personal protective equipment (PPE).<sup>56,73</sup> Although practices improved in subsequent years, problems still exist.<sup>111</sup> In addition, the occupational management of these chemicals has been further clarified. These trends, in conjunction with many information requests, have prompted OSHA to revise its recommendations for hazardous drug handling. In addition, some of these agents are covered under the Hazard Communication Standard (HCS) [Div 2 1910.1200].<sup>107</sup>

In order to provide recommendations consistent with current scientific knowledge, this informational guidance document has been expanded to cover hazardous drugs (HD), in addition to the cytotoxic drugs (CD) that were covered in the 1986 guidelines. The recommendations apply to all settings where employees are occupationally exposed to HDs: such as hospitals, physicians' offices and home health care agencies. It is recognized that sections dealing with work areas and prevention of employee exposure refer to workplaces where pharmaceuticals are used in concentrations appropriate for patient therapy. In those settings where employees work with drugs in a more potentially hazardous form, such as a more concentrated form in some components of pharmaceutical manufacturing, measures that afford employees a greater degree of protection from exposure are commonly employed and should be used.

This review will:

- Provide criteria for classifying drugs as hazardous,
- Summarize the evidence supporting the management of HDs as an occupational hazard,
- Discuss the equipment and worker education recommended as well as the legal requirements of standards for the protection of workers exposed and potentially exposed to HDs,
- Update the important aspects of medical surveillance, and
- List some common HDs currently in use.

Anesthetic agents have not been considered in this review. However, exposure to some of these agents is a recognized health hazard,<sup>104</sup> and they have been considered in a separate Technical Manual Chapter.

## **II. Categorization of Drugs as Hazardous**

The purpose of this section is to describe the biological effects of those pharmaceuticals which are considered hazardous. A number of pharmaceuticals in the health care setting may pose occupational risk to employees through acute and chronic workplace exposure. Past attention focused on drugs used to treat cancer. However, it is clear that many other agents also have toxicity profiles of concern. This recognition prompted the American Society of Hospital

Pharmacists (ASHP) to define a class of agents as "hazardous drugs."<sup>3</sup> That report specified concerns about antineoplastic and non-antineoplastic hazardous drugs in use in most institutions throughout the country. OSHA shares this concern.

## **A. Characteristics**

The **ASHP** Technical Assistance Bulletin (TAB) described four drug characteristics, each of which could be considered hazardous:

- genotoxicity,
- carcinogenicity,
- teratogenicity or fertility impairment, and
- serious organ or other toxic manifestation at low doses in experimental animals or treated patients.

Appendix VI:2-1 of this review lists some common drugs which are considered hazardous by the above criteria. There is no standardized reference for this information nor is there complete consensus on all agents listed.

## **B. Hazard Definition Based on Pharmacology/Toxicology**

Professional judgment by personnel trained in pharmacology/toxicology is essential in designating drugs as hazardous, and reference 65 provides information regarding the development of such a list at one institution. Some drugs, which have a long history of safe use in humans despite in vitro or animal evidence of toxicity, may be excluded by the institution's experts by considerations such as those used to formulate GRAS (Generally Regarded as Safe) lists by the FDA under the Food, Drug, and Cosmetics Act. In contrast, investigational drugs are new chemicals for which there is often little information on potential toxicity. Structure or activity relationships with similar chemicals and in vitro data can be considered in determining potential toxic effects. Investigational drugs should be prudently handled as HDs unless adequate information becomes available to exclude them.

Some major considerations by professionals trained in pharmacology/toxicology<sup>65</sup> in designating a drug as hazardous are:

- Is the drug designated as Therapeutic Category 10:00 (Antineoplastic Agent) in the American Hospital Formulary Service Drug Information?<sup>68</sup>
- Does the manufacturer suggest the use of special isolation techniques in its handling, administration, or disposal?
- Is the drug known to be a human mutagen, carcinogen, teratogen or reproductive toxicant?
- Is the drug known to be carcinogenic or teratogenic in animals (drugs known to be mutagenic in multiple bacterial systems or animals should also be considered hazardous)?

- And, is the drug known to be acutely toxic to an organ system?

Some of the abbreviations used in this review are listed in Table VI:2-1.

Table VI:2-1. **List of Abbreviations**

<b>ANSI</b>	American National Standards Institute
<b>ASHP</b>	American Society of Hospital Pharmacists
<b>BSC</b>	Biological Safety Cabinet
<b>CD</b>	Cytotoxic Drug
<b>EPA</b>	Environmental Protection Agency
<b>HD</b>	Hazardous Drug
<b>HCS</b>	Hazard Communication Standard
<b>HEPA</b>	High Efficiency Particulate Air
<b>IARC</b>	International Agency for Research on Cancer
<b>NIOSH</b>	National Institute for Occupational Safety and Health
<b>NTP</b>	National Toxicology Program
<b>OSHA</b>	Occupational Safety and Health Administration
<b>PPE</b>	Personal Protective Equipment
<b>SDS</b>	Safety Data Sheet

### **III. Background: Hazardous Drugs as Occupational Risks**

Preparation, administration, and disposal of HDs may expose pharmacists, nurses, physicians, and other health care workers to potentially significant workplace levels of these chemicals. The literature establishing these agents as occupational hazards deals primarily with CDs; however, documentation of adverse exposure effects from other HDs is rapidly accumulating.<sup>15,40-43,59</sup> The degree of absorption that takes place during work and the significance of secondary early biological effects on each individual encounter are difficult to assess and may vary depending on the HD. As a result, it is difficult to set safe levels of exposure on the basis of current scientific information. However, there are several lines of evidence supporting the toxic potential of these drugs if handled improperly. Therefore, it is essential to minimize exposure to all HDs. Summary tables of much of the data presented below can be found in Sorsa<sup>95</sup> and Rogers.<sup>84</sup>

#### **A. Mechanism of Action**

Most HDs either bind directly to genetic material in the cell nucleus or affect cellular protein synthesis. Cytotoxic drugs may not distinguish between normal and cancerous cells. The growth and reproduction of the normal cells are often affected during treatment of cancerous cells.

## **B. Animal Data**

Numerous studies document the carcinogenic, mutagenic, and teratogenic effects of HD exposure in animals. They are well summarized in the pertinent IARC publications.<sup>37-43</sup> Alkylating agents present the strongest evidence of carcinogenicity (e.g., cyclophosphamide, mechlorethamine hydrochloride [nitrogen mustard]). However, other classes, such as some antibiotics, have been implicated as well. Extensive evidence for mutagenic and reproductive effects can be found in all antineoplastic classes. The antiviral agent ribavirin has additionally been shown to be teratogenic in all rodent species tested.<sup>31,49</sup> The ASHP recommends that all pharmaceutical agents that are animal carcinogens be handled as human carcinogens.

## **C. Human Data at Therapeutic Levels**

Many HDs are known human carcinogens, for which there is no safe level of exposure. The development of secondary malignancies is a well-documented side-effect of chemotherapy treatment.<sup>52,86,90,115</sup> Leukemia has been most frequently observed. However, other secondary malignancies, such as bladder cancer and lymphoma, have been documented in patients treated for other, usually solid, primary malignancies.<sup>52,114</sup>

Chromosomal aberrations can result from chemotherapy treatment as well. One study, on chlorambucil, reveals chromosomal damage in recipients to be cumulative and related to both dose and duration of therapy.<sup>77</sup>

Numerous case reports have linked chemotherapeutic treatment to adverse reproductive outcomes.<sup>7,88,91,98</sup> Testicular and ovarian dysfunction, including permanent sterility, have occurred in male and female patients who have received HDs either singly or in combination.<sup>14</sup> In addition, some antineoplastic agents are known or suspected to be transmitted to infants through breast milk.<sup>79</sup>

The literature also documents the effects of these drugs on other organ systems. Extravasation of some agents can cause severe soft-tissue injury, consisting of necrosis and sloughing of exposed areas.<sup>23,78,87</sup> Other HDs, such as pentamidine and zidovudine (formerly AZT), are known to have significant side effects (i.e., hematologic abnormalities), in treated patients.<sup>4,33</sup> Serum transaminase elevation has also been reported in treated patients.<sup>4,33</sup>

## **D. Occupational Exposure: Airborne Levels**

Monitoring efforts for cytotoxic drugs have detected measurable air levels when exhaust biological safety cabinets (BSC) were not used for preparation or when monitoring was performed inside the BSC.<sup>50,73</sup>

Concentrations of fluorouracil ranging from 0.12 to 82.26 ng/m<sup>3</sup> have been found during monitoring of drug preparation without a BSC implying an opportunity for respiratory exposure.<sup>73</sup> Elevated concentrations of cyclophosphamide were found by these authors as well. Cyclophosphamide has also been detected on the HEPA filters of flow hoods used in HD preparation, demonstrating aerosolization of the drug and an exposure opportunity mitigated by effective engineering controls.<sup>81</sup>

A recent study has reported wipe samples of cyclophosphamide, one of the class I IARC carcinogens, on surfaces of work stations in an oncology pharmacy and outpatient treatment areas (sinks and countertops). Concentrations ranged from 0.005 to 0.035 mcg/cm<sup>2</sup>, documenting opportunity for dermal exposure.<sup>60</sup>

Administration of drugs via aerosolization can lead to measurable air concentrations in the breathing zone of workers providing treatment. Concentrations up to 18 mcg/m<sup>3</sup> have been found by personal air sampling of workers administering pentamidine.<sup>67</sup> Similar monitoring for ribavirin has found concentrations as high as 316 mcg/m<sup>3</sup>.<sup>31</sup>

## **E. Occupational Exposure: Biological Evidence of Absorption**

### **1. Urinary Mutagenicity**

Falck et al. were the first to note evidence of mutagenicity in the urine of nurses who handled cytotoxic drugs.<sup>26</sup> The extent of this effect increased over the course of the work week. With improved handling practices, a decrease in mutagenic activity was seen.<sup>27</sup> Researchers have also studied pharmacy personnel who reconstitute antineoplastic drugs. These employees showed increasingly mutagenic urine over the period of exposure; when they stopped handling the drugs, activity fell within two days to the level of unexposed controls.<sup>5,76</sup> They also found mutagenicity in workers using horizontal laminar flow BSCs that decreased to control levels with the use of vertical flow containment BSCs.<sup>76</sup>

Other studies have failed to find a relationship between exposure and urine mutagenicity.<sup>25</sup> Sorsa<sup>99</sup> summarizes this information and discusses the factors, such as differences in urine collection timing and variations in the use of PPE, which could lead to disparate results. Differences may also be related to smoking status; smokers exposed to CDs exhibit greater urine mutagenicity than exposed nonsmokers or control smokers suggesting contamination of the work area by CDs and some contribution of smoking to their mutagenic profile.<sup>9</sup>

### **2. Urinary Thioethers**

Urinary thioethers are glutathione conjugated metabolites of alkylating agents which have been evaluated as an indirect means of measuring exposure. Workers who handle cytotoxic drugs have been reported to have increased levels compared to controls and also have increasing thioether levels over a 5-day work week.<sup>44,48</sup> Other studies of nurses who handle CDs and of treated patients have yielded variable results which could be due to confounding by smoking, PPE, and glutathione-S-transferase activity.<sup>11</sup>

### **3. Urinary Metabolites**

Venitt assayed the urine of pharmacy and nursing personnel handling cisplatin and found platinum concentrations at or below the limit of detection for both workers and controls.<sup>112</sup> Hirst found cyclophosphamide in the urine of two nurses who handled the drug documenting worker absorption.<sup>35</sup> (Hirst also documented skin absorption in human volunteers by using gas chromatography after topical application of the drug.) Urinary pentamidine recovery has also been reported in exposed health care workers.<sup>94</sup>

## **F. Occupational Exposure: Human Effects**

### **1. Cytogenetic Effects**

A number of studies have examined the relationship of exposure to CDs in the workplace to chromosomal aberrations. These studies have looked at a variety of markers for damage, including sister chromatid exchanges (SCE), structural aberrations (e.g., gaps, breaks, translocations), and micronuclei in peripheral blood lymphocytes. The results have been somewhat conflicting. Several authors found increases in one or more markers.<sup>74,75,80,113</sup> Increased mutation frequency has been reported as well.<sup>17</sup>

Other studies have failed to find a significant difference between workers and controls.<sup>99,101</sup> Some researchers have found higher individual elevations<sup>28</sup> or a relationship between number of drugs handled and SCEs.<sup>8</sup> These disparate results are not unexpected. The difficulties in quantitating exposure have resulted in different exposure magnitudes between studies; workers in several negative studies appear to have a lower overall exposure.<sup>101</sup> In addition, differences in the use of PPE and work technique will alter absorption of CDs and resultant biologic effects.

Finally, techniques for SCE measurement may not be optimal. A recent study that looked at correlation of phosphoramidate-induced SCE levels with duration of anticancer drug handling found a statistically significant correlation coefficient of zero.<sup>63,66</sup> Taken together, the evidence indicates an excess of markers of mutagenic exposure in unprotected workers.

### **2. Reproductive Effects**

Reproductive effects associated with occupational exposure to CDs have been well documented. Hemminki et al.<sup>32</sup> found no difference in exposure between nurses who had spontaneous abortions and those who had normal pregnancies. However, the study group consisted of nurses who were employed in surgical or medical floors of a general hospital. When the relationship between CD exposure and congenital malformations was explored, the study group was expanded to include oncology nurses, among others, and an odds ratio of 4.7 was found for exposures of more than once per week. This observed odds ratio is statistically significant.

Selevan et al.<sup>89</sup> found a relationship between CD exposure and spontaneous abortion in a case-control study of Finnish nurses. This well designed study reviewed the reproductive histories of 568 women (167 cases) and found a statistically significant odds ratio of 2.3. Similar results were obtained in another large case-control study of French nurses,<sup>102</sup> and a study of Baltimore area nurses found a significantly higher proportion of adverse pregnancy outcomes when exposure to antineoplastic agents occurred during the pregnancy.<sup>85</sup> The nurses involved in these studies usually prepared and administered the drugs. Therefore, workplace exposure of these groups of professionals to such products has been associated with adverse reproductive outcomes in several investigations.

### **3. Other Effects**

Hepatocellular damage has been reported in nurses working in an oncology ward; the injury appeared to be related to intensity and duration of work exposure to CDs.<sup>96</sup> Symptoms such as

lightheadedness, dizziness, nausea, headache, and allergic reactions have also been described in employees after the preparation and administration of antineoplastic drugs in unventilated areas.<sup>22,86</sup> In occupational settings, these agents are known to be toxic to the skin and mucous membranes, including the cornea.<sup>69, 82</sup>

Pentamidine has been associated with respiratory damage in one worker who administered the aerosol. The injury consisted of a decrease in diffusing capacity that improved after exposure ceased.<sup>29</sup> The onset of bronchospasm in a pentamidine-exposed worker has also been reported.<sup>22</sup> Employees involved in the aerosol administration of ribavirin have noted symptoms of respiratory tract irritation.<sup>55</sup> A number of medications including psyllium and various antibiotics are known respiratory and dermal sensitizers. Exposure in susceptible individuals can lead to asthma or allergic contact dermatitis.

## **IV. Work Areas**

Risks to personnel working with HDs are a function of the drugs inherent toxicity and the extent of exposure. The main routes of exposure are: inhalation of dusts or aerosols, dermal absorption, and ingestion. Contact with contaminated food or cigarettes represents the primary means of ingestion. Opportunity for exposure to HDs may occur at many points in the handling of these drugs.

### **A. Pharmacy or Other Preparation Areas**

In large oncology centers, HDs are usually prepared in the pharmacy. However, in small hospitals, outpatient treatment areas, and physicians' offices they have been prepared by physicians or nurses without appropriate engineering controls and protective apparel.<sup>16,20</sup> Many HDs must be reconstituted, transferred from one container to another, or manipulated before administration to patients. Even if care is taken, opportunity for absorption through inhalation or direct skin contact can occur.<sup>35,36,73,116</sup>

Examples of manipulations that can cause splattering, spraying, and aerosolization include:

- withdrawal of needles from drug vials,
- drug transfer using syringes and needles or filter straws,
- breaking open of ampules, and
- expulsion of air from a drug-filled syringe.

Evaluation of these preparation techniques, using fluorescent dye solutions, has shown contamination of gloves and the sleeves and chest of gowns.<sup>97</sup>

Horizontal airflow work benches provide an aseptic environment for the preparation of injectable drugs. However, these units provide a flow of filtered air originating at the back of the work space and exiting toward the employee using the unit. Thus, they increase the likelihood of drug

exposure to both the preparer and other personnel in the room. As a result, the use of horizontal BSCs is contraindicated in the preparation of HDs. Smoking, drinking, applying cosmetics, and eating where these drugs are prepared, stored, or used also increase the chance of exposure.

## **B. Administration of Drugs to Patients**

Administration of drugs to patients is generally performed by nurses or physicians. Drug injection into the IV line, clearing of air from the syringe or infusion line, and leakage at the tubing, syringe, or stopcock connection present opportunities for skin contact and aerosol generation. Clipping used needles and crushing used syringes can produce considerable aerosolization as well.

Such techniques where needles and syringes are contaminated with blood or other potentially infectious material are prohibited by the Bloodborne Pathogens Standard.<sup>109</sup> Prohibition of clipping or crushing of any needle or syringe is sound practice.

Excreta from patients who have received certain antineoplastic drugs may contain high concentrations of the drug or its hazardous metabolites. For example, patients receiving cyclophosphamide excrete large amounts of the drug and its mutagenic metabolites.<sup>46,92</sup> Patients treated with cisplatin have been shown to excrete potentially hazardous amounts of the drug.<sup>112</sup> Unprotected handling of urine or urine-soaked sheets by nursing or housekeeping personnel poses a source of exposure.

## **C. Disposal of Drugs and Contaminated Materials**

Contaminated materials used in the preparation and administration of HDs, such as gloves, gowns, syringes and vials, present a hazard to support and housekeeping staff. The use of properly labeled, sealed and covered disposal containers, handled by trained and protected personnel, should be routine, and is required under the Bloodborne Pathogens Standard<sup>109</sup> if such items are contaminated with blood or other potentially infectious materials. HDs and contaminated materials should be disposed of in accordance with federal, state, and local laws. Disposal of some of these drugs is regulated by the EPA. Those drugs which are unused commercial chemical products and are considered by the EPA to be toxic wastes must be disposed of in accordance with 40CFR part 261.<sup>33,24</sup> Spills can also represent a hazard; the employer should ensure that all employees are familiar with appropriate spill procedures.

## **D. Survey of Current Work Practices**

Surveys of U.S. cancer centers and oncology clinics reveal wide variation in work practices, equipment or training for personnel preparing CDs.<sup>56,73</sup> This lack of standardization results in a high prevalence of potential occupational exposure to CDs. One survey found that 40% of hospital pharmacists reported a skin exposure to CDs at least once a month, and only 28% had medical surveillance programs in their workplaces.<sup>16</sup> Nurses, particularly those in outpatient settings, were found to be even less well protected than pharmacists.<sup>111</sup> Such findings emphasize current lack of protection for all personnel who risk potential exposure to HDs.

## V. Prevention of Employee Exposure

### **A. Hazardous Drug Safety and Health Plan**

Where hazardous drugs, as defined in this review, are used in the workplace, sound practice would dictate that a written *Hazardous Drug Safety and Health Plan* be developed. Such a plan assists in:

- Protecting employees from health hazards associated with HDs, and
- Keeping exposures as low as reasonably achievable.

When a *Hazardous Drug Safety and Health Plan* is developed, it should be readily available and accessible to all employees, including temporary employees, contractors, and trainees. The ASHP recommends that the *Plan* include each of the following elements and indicate specific measures that the employer is taking to ensure employee protection:<sup>3</sup>

- Standard operating procedures relevant to safety and health considerations to be followed when health care workers are exposed to hazardous drugs,
- Criteria that the employer uses to determine and implement control measures to reduce employee exposure to hazardous drugs including engineering controls, the use of personal protective equipment, and hygiene practices,
- A requirement that ventilation systems and other protective equipment function properly, and specific measures to ensure proper and adequate performance of such equipment,
- Provision for information and training,
- The circumstances under which the use of specific HDs (that is, FDA investigational drugs) require prior approval from the employer before implementation,
- Provision for medical examinations of potentially exposed personnel, and
- Designation of personnel responsible for implementation of the *Hazardous Drug Safety and Health Plan* including the assignment of a *Hazardous Drug Officer* (who is an industrial hygienist, nurse, or pharmacist health and safety representative); and, if appropriate, establishment of a Hazardous Drug Committee or a joint Hazardous Drug Committee/Chemical Committee.

The ASHP further recommends that specific consideration of the following provisions be included where appropriate:

- Establishment of a designated **HD** handling area,
- Use of containment devices such as biological safety cabinets,
- Procedures for safe removal of contaminated waste, and
- Decontamination procedures.

The ASHP recommends that the *Hazardous Drug Safety and Health Plan* be reviewed and its effectiveness reevaluated at least annually and updated as necessary.

A comparison of OSHA 300 log entries to employee medical clinic appointment or visit rosters can be made<sup>3</sup> to establish if there is evidence of disorders that could be hazardous drug related. Previous health and safety inspections by local health departments, fire departments, regulatory, or accrediting agencies may be helpful for the facility's planning purposes as well as any OSHA review of hazards and programs in the facility. Joint Commission on Accreditation of Healthcare Organizations (JCAHO), or College of American Pathologists (CAP) review of facilities may contain information on hazardous drugs used in the facility.

## **B. Drug Preparation Precautions**

### **1. Work Area**

The ASHP recommends that HD preparation be performed in a restricted, preferably, centralized area. Signs restricting the access of unauthorized personnel are to be prominently displayed. Eating, drinking, smoking, chewing gum, applying cosmetics, and storing food in the preparation area should be prohibited.<sup>71</sup> The ASHP recommends that procedures for spills and emergencies, such as skin or eye contact, be available to workers, preferably posted in the area.<sup>3</sup>

### **2. Biological Safety Cabinets**

Class II or III Biological Safety Cabinets (BSC) that meet the current National Sanitation Foundation Standard<sup>49,70,72</sup> should minimize exposure to HDs during preparation. Although these cabinets are designed for biohazards, several studies have documented reduced urine mutagenicity in CD-exposed workers or reduced environmental levels after the institution of BSCs.<sup>5,51,61</sup> If a BSC is unavailable, for example in private practice office, accepted practice is the sharing of a cabinet (e.g., several medical offices share a cabinet) or sending the patient to a center where HDs can be prepared in a BSC. Alternatively, preparation can be performed in a facility with a BSC and the drugs transported to the area of administration. Use of a dedicated BSC, where only HDs are prepared, is prudent practice.

### **3. Types of BSC's**

Four main types of Class II BSCs are available. They all have downward airflow and HEPA filters. They are differentiated by the amount of air recirculated within the cabinet, whether this air is vented to the room or the outside, and whether contaminated ducts are under positive or negative pressure. These four types are:

- Type A cabinets recirculate approximately 70% of cabinet air through HEPA filters back into the cabinet; the rest is discharged through a HEPA filter into the preparation room. Contaminated ducts are under positive pressure.
- Type B1 cabinets have higher velocity air inflow, recirculate 30% of the cabinet air, and exhaust the rest to the outside through HEPA filters. They have negative-pressure contaminated ducts and plenums.

- Type B2 systems are similar to Type B1 except that no air is recirculated.
- Type B3 cabinets are similar to Type A in that they recirculate approximately 70% of cabinet air. However, the other 30% is vented to the outside and the ducts are under negative pressure.

Class III cabinets are totally enclosed with gas tight construction. The entire cabinet is under negative pressure, and operations are performed through attached gloves. All air is HEPA filtered.

Class II, type B, or Class III BSCs are recommended since they vent to the outside.<sup>3</sup> Those without air recirculation are the most protective. If the BSC has an outside exhaust, it should be vented away from air intake units.

The exhaust fan or blower on the vertical airflow hood should be on at all times, except when the hood is being mechanically repaired or moved. If the blower is turned off, the hood should be decontaminated before reuse.<sup>3,72</sup> Each BSC should be equipped with a continuous monitoring device to allow confirmation of adequate air flow and cabinet performance. The cabinet should be in an area with minimal air turbulence; this will reduce leakage to the environment.<sup>6,70</sup> Additional information on design and performance testing of BSCs can be found in papers by Avis and Levchuck,<sup>6</sup> Bryan and Marback,<sup>10</sup> and the National Sanitation Foundation.<sup>70</sup> Practical information regarding space needs and use of BSCs is contained in the ASHP's 1990 technical assistance bulletin.<sup>3</sup>

Ventilation and biosafety cabinets installed should be maintained and evaluated for proper performance in accordance with the manufacturer's instructions.

#### **4. Decontamination**

The cabinet should be cleaned according to the manufacturer's instructions. Some manufacturers have recommended weekly decontamination, as well as whenever spills occur, or when the cabinet requires moving, service or certification.

Decontamination should consist of surface cleaning with water and detergent followed by thorough rinsing. The use of detergent is recommended because there is no single accepted method of chemical deactivation for all agents involved.<sup>13,45</sup> Quaternary ammonium cleaners should be avoided due to the possibility of vapor build-up in recirculated air.<sup>3</sup> Ethyl alcohol or 70% isopropyl alcohol may be used with the cleaner if the contamination is soluble only in alcohol.<sup>3</sup> Alcohol vapor build-up has also been a concern, so the use of alcohol should be avoided in BSCs where air is recirculated.<sup>3</sup> Spray cleaners should also be avoided due to the risk of spraying the HEPA filter. Ordinary decontamination procedures, which include fumigation with a germicidal agent, are inappropriate in a BSC used for HDs because such procedures do not remove or deactivate the drugs.

Removable work trays, if present, should be lifted in the BSC so the back and any sump below can be cleaned. During cleaning, the worker should wear PPE similar to that used for spills. *Ideally, the sash should remain down during cleaning, however, a NIOSH-approved respirator*

*appropriate for the hazard must be worn by the worker if the sash will be lifted during the process.* The exhaust fan/blower should be left on. Cleaning should proceed from least to most contaminated areas. The drain spillage trough area should be cleaned at least twice since it can be heavily contaminated. All materials from the decontamination process should be handled as HDs and disposed of in accordance with Federal, State, and local laws.

## **5. Service and Certification**

The ASHP recommends that BSCs be serviced and certified by a qualified technician every 6 months or any time the cabinet is moved or repaired.<sup>3,71</sup> Technicians servicing these cabinets or changing the HEPA filters should be aware of HD risks through hazard communication training from their employers and should use the same personal protective equipment as recommended for large spills.

Certification of the BSC includes performance testing as outlined in the procedures of the National Sanitation Foundation's Standard Number 49.<sup>70</sup> Helpful information on such testing can be found in the ASHP 1990 technical assistance bulletins,<sup>3</sup> the BSC manufacturer's equipment manuals, and Bryan and Marback's paper.<sup>10</sup> HEPA filters should be changed when they restrict airflow or if they are contaminated by an accidental spill. They should be bagged in plastic and disposed of as HDs. Any time the cabinet is turned off or transported it should be sealed with plastic.

## **6. Personal Protective Equipment**

### **GLOVES**

Research indicates that the thickness of the gloves used in handling HDs is more important than the type of material since all materials tested have been found to be permeable to some HDs.<sup>3, 19, 53</sup> The best results are seen with latex gloves. Therefore, latex gloves should be used for the preparation of HDs unless the drug-product manufacturer specifically stipulates that some other glove provides better protection.<sup>19,53,72,93,100</sup> Thicker, longer latex gloves that cover the gown cuff are recommended for use with HDs. Gloves with minimal or no powder are preferred since the powder may absorb contamination.<sup>3, 104</sup>

The above referenced sources have noted great variability in permeability within and between glove lots. Therefore, double gloving is recommended if it does not interfere with an individual's technique.<sup>3</sup> Because all gloves are permeable to some extent and their permeability increases with time, they should be changed regularly (hourly) or immediately if they are torn, punctured, or contaminated with a spill. Hands should always be washed before gloves are put on and after they are removed. Employees need thorough training in proper methods for contaminated glove removal.

### **GOWNS**

A protective disposable gown made of lint-free, low-permeability fabric with a closed front, long sleeves, and elastic or knit closed cuffs should be worn. The cuffs should be tucked under the gloves. If double gloves are worn, the outer glove should be over the gown cuff and the inner

glove should be under the gown cuff. When the gown is removed, the inner glove should be removed last. Gowns and gloves in use in the HD preparation area should not be worn outside the HD preparation area.<sup>3</sup>

As with gloves, there is no ideal material. Research has found nonporous Tyvek and Kaycel to be more permeable than Saranex-laminated Tyvek and polyethylene-coated Tyvek after 4 hours of exposure to the CDs tested.<sup>54</sup> However, little airflow is allowed with the latter materials. As a result, manufacturers have produced gowns with Saranex or polyethylene reinforced sleeves and front in an effort to decrease permeability in the most exposure prone areas, but little data exists on decreasing exposure.

## **RESPIRATORY PROTECTION**

A BSC is essential for the preparation of HDs. Where a BSC is not currently available, a NIOSH-approved respirator\* [*\* NIOSH recommendation at the time of this publication is for a respirator with a high-efficiency filter, preferably a powered air-purifying respirator*] appropriate for the hazard must be worn to afford protection until the BSC is installed. The use of respirators must comply with OSHA's Respiratory Protection Standard<sup>105</sup> which outlines the aspects of a respirator program, including selection, fit testing, and worker training. Surgical masks are not appropriate since they do not prevent aerosol inhalation.

Permanent respirator use, in lieu of BSCs, is imprudent practice and should not be a substitute for engineering controls.

## **EYE and FACE PROTECTION**

Whenever splashes, sprays or aerosols of HDs may be generated, which can result in eye, nose, or mouth contamination, chemical-barrier face and eye protection must be provided and used in accordance with OAR 437-002-0134. Eyeglasses with temporary side shields are inadequate protection.

When a respirator is used to provide temporary protection as described above, and splashes, sprays, or aerosols are possible, employee protection should be:

- a respirator with a full face piece, or
- a plastic face shield or splash goggles complying with ANSI standards<sup>2</sup> when using a respirator of less than full face piece design.

Eyewash facilities should also be made available.

## **PPE DISPOSAL and DECONTAMINATION**

All gowns, gloves, and disposable materials used in preparation should be disposed of according to the hospital's hazardous drug waste procedures and as described under this review's section on Waste Disposal. Goggles, face shields and respirators may be cleaned with mild detergent and water for reuse.

## C. Work Equipment

NIH has recommended that work with HDs be carried out in a BSC on a disposable, plastic-backed paper liner. The liner should be changed after preparation is completed for the day or after a shift, whichever comes first. Liners should also be changed after a spill.<sup>103</sup> Syringes and IV sets with Luer-lock fittings should be used for HDs. Syringe size should be large enough so that they are not full when the entire drug dose is present.

A covered disposable container should be used to contain excess solution. A covered sharps container should be in the BSC. The ASHP recommends that HD-labeled plastic bags be available for all contaminated materials (including gloves, gowns, and paper liners), so that contaminated material can be immediately placed in them and disposed of in accordance with ASHP recommendations.<sup>3</sup>

### 1. Work Practices

Correct work practices are essential to worker protection. Aseptic technique is assumed as a standard practice in drug preparation. The general principles of aseptic technique, therefore, will not be detailed here. It should be noted, however, that BSC benches differ from horizontal flow units in several ways that require special precautions. Manipulations should not be performed close to the work surface of a BSC. Unsterilized items, including liners and hands, should be kept downstream from the working area.

Entry and exit of the cabinet should be perpendicular to the front. Rapid lateral hand movements should be avoided. Additional information can be found in the National Sanitation Foundation Standard 49 for Class II (Laminar Flow) Biohazard Cabinetry<sup>70</sup> and Avis and Levchuck's paper.<sup>6</sup> All operators should be trained in these containment area protocols. All PPE should be donned before work is started in the BSC. All items necessary for drug preparation should be placed within the BSC before work is begun. Extraneous items should be kept out of the work area.

### LABELING

In addition to standard pharmacy labeling practices, all syringes and IV bags containing HDs should be labeled with a distinctive warning label such as:

<b>SPECIAL HANDLING/DISPOSAL PRECAUTIONS</b>
--

In addition, those HDs covered under HCS must have labels in accordance with section (f) of the standard to warn employees handling the drug(s) of the hazards.

### NEEDLES

The ASHP recommends that all syringes and needles used in the course of preparation be placed in "*sharps*" containers for disposal without being crushed, clipped or capped.<sup>3,103</sup>

## **PRIMING**

Prudent practice dictates that drug administration sets be attached and primed within the BSC, prior to addition of the drug. This eliminates the need to prime the set in a less well controlled environment and ensures that any fluid that escapes during priming contains no drug. If priming must occur at the site of administration, the intravenous line should be primed with non-drug containing fluid or a back-flow closed system should be used.<sup>3</sup>

## **HANDLING VIALS**

Extremes of positive and negative pressure in medication vials should be avoided, e.g., attempting to withdraw 10 cc of fluid from a 10-cc vial or placing 10 cc of a fluid into an air-filled 10-cc vial.

The use of large-bore needles, #18 or #20, avoids *high-pressure syringing* of solutions. However, some experienced personnel believe that large-bore needles are more likely to drip. Multiuse dispensing pins are recommended to avoid these problems.

Venting devices such as filter needles or dispensing pins permit outside air to replace the withdrawn liquid. Proper worker education is essential before using these devices.<sup>3</sup> Although venting devices are recommended, another technique is to add diluent slowly to the vial by alternately injecting small amounts and allowing displaced air to escape into the syringe. When all diluent has been added, a small amount of additional air may be withdrawn to create a slight negative pressure in the vial. This should not be expelled into room air because it may contain drug residue. It should either be injected into a vacuum vial or remain in the syringe to be discarded.

If any negative pressure must be applied to withdraw a dosage from a stoppered vial and handling safety is compromised, an air-filled syringe should be used to equalize pressure in the stoppered vial. The volume of drug to be withdrawn can be replaced by injecting small amounts of air into the vial and withdrawing equal amounts of liquid until the required volume is withdrawn. The drug should be cleared from the needle and hub (neck) of the syringe before separating to reduce spraying on separation.

## **HANDLING AMPULES**

Prudent practice requires that ampules with dry material should be "*gently tapped down*" before opening to move any material in the top of the ampule to the bottom quantity. A sterile gauze pad should be wrapped around the ampule neck before breaking the top.<sup>3</sup> This can protect against cuts and catch airborne powder or aerosol. If diluent is to be added, it should be injected slowly down the inside wall of the ampule. The ampule should be tilted gently to ensure that all the powder is wet before agitating it to dissolve the contents.

After the solution is withdrawn from the ampule with a syringe, the needle should be cleared of solution by holding it vertically with the point upwards; the syringe should be tapped to remove air bubbles. Any bubbles should be expelled into a closed container.

## **PACKAGING HDs for TRANSPORT**

The outside of bags or bottles containing the prepared drug should be wiped with moist gauze. Entry ports should be wiped with moist alcohol pads and capped. Transport should occur in sealed plastic bags and transported in containers designed to avoid breakage.

HDs that are shipped and which are subject to EPA regulation as hazardous waste are also subject to Department of Transportation (DOT) regulations as specified in 49CFR part 172.101.

## **NONLIQUID HDs**

The handling of nonliquid forms of HDs requires special precautions as well.

Tablets which may produce dust or potential exposure to the handler should be counted in a BSC. Capsules, i.e., gel-caps or coated tablets, are unlikely to produce dust unless broken in handling.

These are counted in a BSC on equipment designated for HDs only, because even manual counting devices may be covered with dust from the drugs handled. Automated counting machines should not be used unless an enclosed process isolates the hazard from the employee(s).

Compounding should also occur in a BSC. A gown and gloves should be worn. *(If a BSC is unavailable, an appropriate NIOSH-approved respirator must be worn.)*

## **2. Drug Administration**

### **PERSONAL PROTECTIVE EQUIPMENT**

The National Study Commission on Cytotoxic Exposure has recommended that personnel administering HDs wear gowns, latex gloves, and chemical splash goggles or equivalent safety glasses as described under the PPE section, preparation.<sup>71</sup> *NIOSH-approved respirators should be worn when administering aerosolized drugs.*

### **ADMINISTRATION KIT**

Protective and administration equipment may be packaged together and labeled as a HD administration kit. Such a kit could include:

- personal protective equipment,
- gauze (4" x 4") for cleanup,
- alcohol wipes,
- disposable plastic-backed absorbent liner,
- puncture-resistant container for needles and syringes,
- a thick sealable plastic bag (with warning label), and

- accessory warning labels.

## **WORK PRACTICES**

Safe work practices when handling HDs should include:

- Hands should be washed before donning and after removing gloves. Gowns or gloves that become contaminated should be changed immediately. Employees should be trained in proper methods to remove contaminated gloves and gowns. After use, gloves and gowns should be disposed of in accordance with ASHP recommendations.
- Infusion sets and pumps, which should have Luer-lock fittings, should be observed for leakage during use. A plastic-backed absorbent pad should be placed under the tubing during administration to catch any leakage. Sterile gauze should be placed around any push sites; IV tubing connection sites should be taped.
- Priming IV sets or expelling air from syringes should be carried out in a BSC. If done at the administration site, ASHP recommends that the line be primed with non-drug containing solution or that a back-flow closed system be used. IV containers with venting tubes should not be used.<sup>3</sup>
- Syringes, IV bottles and bags, and pumps should be wiped clean of any drug contamination with sterile gauze. Needles and syringes should not be crushed or clipped. They should be placed in a puncture-resistant container, then into the HD disposal bag with all other HD-contaminated materials.
- Administration sets should be disposed of intact. Disposal of the waste bag should follow HD disposal requirements. Unused drugs should be returned to the pharmacy.
- Protective goggles should be cleaned with detergent and properly rinsed. All protective equipment should be disposed of upon leaving the patient care area.
- Nursing stations where these drugs will be administered should have spill and emergency skin and eye decontamination kits available and relevant SDSs for guidance. The HCS requires SDSs to be readily available in the workplace to all employees working with hazardous chemicals.
- PPE should be used during the administration of oral HDs if splashing is possible.

A large number of investigational HDs are under clinical study in health care facilities. Personnel not directly involved in the investigation should not administer these drugs unless they have received adequate instructions regarding safe handling procedures. Literature regarding potential toxic effects of investigational drugs should be evaluated prior to the drug's introduction into the workplace.<sup>65</sup>

The increased use of HDs in the home environment necessitates special precautions. Employees involved in home care delivery should follow the above work practices and employers should make administration and spill kits available. Home health care workers should have emergency

protocols with them as well as phone numbers and addresses in the event emergency care becomes necessary.<sup>3</sup> Waste disposal for drugs delivered for home use and other home contaminated material should also be considered by the employer and should follow applicable regulations.

## **AEROSOLIZED DRUGS**

The administration of aerosolized HDs requires special engineering controls to prevent exposure to health care workers and others in the vicinity. In the case of *pentamidine*, these controls include treatment booths with local exhaust ventilation designed specifically for its administration. A variety of ventilation methods have also been used for the administration of *ribavirin*. These include isolation rooms with separate HEPA filtered ventilation systems and administration via endotracheal tube.<sup>30, 47</sup> Engineering controls used to manage employee exposure to anesthetic gases is a traditional example of occupational chemical management. Both isolation and ventilation are used for these volatile HDs.

### **3. Caring for Patients Receiving HDs**

In accordance with the Bloodborne Pathogens Standard, universal precautions must be observed to prevent contact with blood or other potentially infectious materials. Under circumstances in which differentiation between body fluid types is difficult or impossible, all body fluids should be considered potentially infectious materials and must be managed as dictated in the Bloodborne Pathogens Standard.<sup>109</sup>

## **PERSONAL PROTECTIVE EQUIPMENT**

Personnel dealing with excreta, primarily urine, from patients who have received HDs in the last 48 hours should be provided with and wear latex or other appropriate gloves and disposable gowns, to be discarded after each use or whenever contaminated, as detailed under Waste Disposal. Eye protection should be worn if splashing is possible. Such excreta contaminated with blood, or other potentially infectious materials as well, should be managed according to the Bloodborne Pathogen Standard. Hands should be washed after removal of gloves or after contact with the above substances.

## **LINEN**

Linen contaminated with HDs or excreta from patients who have received HDs in the past 48 hours is a potential source of exposure to employees. Linen soiled with blood or other potentially infectious materials as well as contaminated with excreta must also be managed according to the Bloodborne Pathogens Standard.<sup>109</sup> Linen contaminated with HDs should be placed in specially marked laundry bags and then placed in a labeled impervious bag. The laundry bag and its contents should be prewashed, and then the linens added to other laundry for a second wash. Laundry personnel should wear latex gloves and gowns while handling prewashed material.

## **REUSABLE ITEMS**

Glassware or other contaminated reusable items should be washed twice with detergent, by a trained employee wearing double latex gloves and a gown.

## 4. Waste Disposal

### EQUIPMENT

Thick, leak-proof plastic bags, colored differently from other hospital trash bags, should be used for routine accumulation and collection of used containers, discarded gloves, gowns, and any other disposable material. Bags containing hazardous chemicals (as defined by Section C of HCS), shall be labeled in accordance with Section F of the Hazard Communication Standard where appropriate. Where the Hazard Communication Standard does not apply, labels should indicate that bags contain HD-related wastes.

Needles, syringes, and breakable items not contaminated with blood or other potentially infectious materials should be placed in a "*sharps*" container before they are stored in the waste bag. Such items that *are* contaminated with blood or other potentially infectious material *must* be placed in a "*sharps*" container. Similarly, needles should not be clipped or capped nor syringes crushed. If contaminated by blood or other potentially infectious material, such needles/syringes *must not* be clipped, capped, or crushed (except as on a rare instance where a *medical* procedure requires recapping). The waste bag should be kept inside a covered waste container clearly labeled "*HD Waste Only.*" At least one such receptacle should be located in every area where the drugs are prepared or administered. Waste should not be moved from one area to another. The bag should be sealed when filled and the covered waste container taped.

### DISPOSAL

Hazardous drug-related wastes should be handled separately from other hospital trash and disposed of in accordance with applicable EPA, state, and local regulations for hazardous waste.<sup>24,110</sup> This disposal can occur at either an incinerator or a licensed sanitary landfill for toxic wastes, as appropriate. Commercial waste disposal is performed by a licensed company. While awaiting removal, the waste should be held in a secure area in covered, labeled drums with plastic liners.

Chemical inactivation traditionally has been a complicated process that requires specialized knowledge and training. The SDS should be consulted regarding specific advice on cleanup. IARC<sup>13</sup> and Lunn et al.<sup>58</sup> have validated inactivation procedures for specific agents that are effective. However, these procedures vary from drug to drug and may be impractical for small amounts. Care must be taken because of unique problems presented by the cleanup of some agents, such as by-product formation.<sup>57</sup> Serious consideration should be given to alternative disposal methods.

## 5. Spills

Emergency procedures to cover spills or inadvertent release of hazardous drugs should be included in the facility's overall health and safety program. Incidental spills and breakages should be cleaned up immediately by a properly protected person trained in the appropriate procedures. The area should be identified with a warning sign to limit access to the area. Incident Reports should be filed to document the spill and those exposed.

## PERSONNEL CONTAMINATION

Contamination of protective equipment or clothing, or direct skin or eye contact should be treated by:

- Immediately removing the gloves or gown,
- Immediate cleansing of the affected skin with soap and water,
- Flooding an affected eye at an eyewash fountain or with water or isotonic eyewash designated for that purpose for at least 15 minutes, for eye exposure,
- Obtaining 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.), and
- Documenting the exposure in the employee's medical record.

## CLEANUP OF SMALL SPILLS

The ASHP considers small spills to be those less than 5 ml. The 5-ml volume of material should be used to categorize spills as large or small. Spills of less than 5 ml or 5 gm outside a BSC should be cleaned up immediately by personnel wearing gowns, double latex gloves, and splash goggles. *An appropriate NIOSH-approved respirator should be used for either powder or liquid spills where airborne powder or aerosol is or has been generated.*

- Liquids should be wiped with absorbent gauze pads; solids should be wiped with wet absorbent gauze. The spill areas should then be cleaned three times using a detergent solution followed by clean water.
- Any broken glass fragments should be picked up using a small scoop (never the hands) and placed in a "sharps" container. The container should then go into a HD disposal bag, along with used absorbent pads and any other contaminated waste.
- Contaminated reusable items, for example glassware and scoops, should be treated as outlined above under Reusable Items.

## CLEANUP OF LARGE SPILLS

When a large spill occurs, the area should be isolated and aerosol generation avoided. For spills larger than 5 ml, liquid spread is limited by gently covering with absorbent sheets or spill-control pads or pillows. If a powder is involved, damp cloths or towels should be used. Specific individuals should be trained to clean up large spills.

Protective apparel, including respirators, should be used as with small spills when there is any suspicion of airborne powder or that an aerosol has been or will be generated. Most CDs are not volatile; however, this may not be true for all HDs. The volatility of the drug should be assessed in selecting the type of respiratory protection.

As discussed under waste disposal, chemical inactivation should be avoided in this setting.

All contaminated surfaces should be thoroughly cleaned three times with detergent and water. All contaminated absorbent sheets and other materials should be placed in the HD disposal bag.

## **SPILLS IN BSCs**

Extensive spills within a BSC necessitate decontamination of all interior BSC surfaces after completion of the spill cleanup. The ASHP<sup>3</sup> recommends this action for spills larger than 150 ml or the contents of one vial. If the HEPA filter of a BSC is contaminated, the unit should be labeled and sealed in plastic until the filter can be changed and disposed of properly by trained personnel wearing appropriate protective equipment.

## **SPILL KITS**

Spill kits, clearly labeled, should be kept in or near preparation and administrative areas. The SDSs include sections on emergency procedures, including appropriate personal protective equipment. The ASHP<sup>3</sup> recommends that kits include: chemical splash goggles, 2 pairs of gloves, utility gloves, a low-permeability gown, 2 sheets (12" x 12") of absorbent material, 250-ml and 1-liter spill control pillows, a "*sharps*" container, a small scoop to collect glass fragments, and 2 large HD waste-disposal bags.<sup>3</sup>

Prior to cleanup, appropriate protective equipment should be donned. Absorbent sheets should be incinerable. Protective goggles and respirators should be cleaned with mild detergent and water after use.

## **6. Storage and Transport**

### **STORAGE AREAS**

Access to areas where HDs are stored should be limited to authorized personnel with signs restricting entry.<sup>72</sup> A list of drugs covered by HD policies and information on spill and emergency contact procedures should be posted or easily available to employees. Optimally, facilities used for storing HDs should not be used for other drugs, and such facilities should be designed to prevent containers from falling to the floor, e.g., bins with barrier fronts. Warning labels should be applied to all HD containers, as well as the shelves and bins where these containers are permanently stored.

### **RECEIVING DAMAGED HD PACKAGES**

Damaged shipping cartons should be opened in an isolated area or a BSC by a designated employee wearing double gloves, a gown, goggles, and appropriate respiratory protection. Individuals must be trained to process damaged packages as well.

The ASHP recommends that broken containers and contaminated packaging mats be placed in a "*sharps*" container and then into HD disposal bags.<sup>3</sup> The bags should then be closed and placed in receptacles as described under Waste Disposal.

The appropriate protective equipment and waste disposal materials should be kept in the area where shipments are received, and employees should be trained in their use and the risks of exposure to HDs.

## **TRANSPORT**

HDs should be securely capped or sealed, placed in sealed clear plastic bags, and transported in containers designed to avoid breakage.

Personnel involved in transporting HDs should be trained in spill procedures, including sealing off the contaminated area and calling for appropriate assistance.

All HD containers should be labeled as noted in Drug Preparation Work Practices. If transport methods that produce stress on contents (such as pneumatic tubes) are used, guidance from the OSHA clarification of 1910.1030 with respect to transport (M.4.b.(8)(c)) should be followed. This clarification provides for use of packaging material inside the tube to prevent breakage. These recommendations that pertain to the Bloodborne Pathogens Standard are prudent practice for HDs, e.g., padded inserts for carriers.

## **VI. Medical Surveillance**

Workers who are potentially exposed to chemical hazards should be monitored in a systematic program of medical surveillance intended to prevent occupational injury and disease.<sup>3, 71, 72</sup> The purpose of surveillance is to identify the earliest reversible biologic effects so that exposure can be reduced or eliminated before the employee sustains irreversible damage. The occurrence of exposure-related disease or other adverse health effects should prompt immediate re-evaluation of primary preventive measures (e.g., engineering controls, personal protective equipment). In this manner, medical surveillance acts as a check on the appropriateness of controls already in use.<sup>62</sup>

For detection and control of work-related health effects, *job-specific* medical evaluations should be performed:

- before job placement,
- periodically during employment,
- following acute exposures, and
- at the time of job termination or transfer (exit examination).

This information should be collected and analyzed in a systematic fashion to allow early detection of disease patterns in individual workers and groups of workers.

## **A. Pre-placement Medical Examinations**

Sound medical practice dictates that employees who will be working with HDs in the workplace have an initial evaluation consisting of a history, physical exam, and laboratory studies. Information made available, by the employer, to the examining physician should be:

- a description of the employee's duties as they relate to the employee's exposure, the employee's exposure levels or anticipated exposure levels,
- a description of any personal protective equipment used or to be used, and
- information from previous medical examinations of the employee, which is not readily available to the examining physician.

The history details the individual's medical and reproductive experience with emphasis on potential risk factors, such as past hematopoietic, malignant, or hepatic disorders. It also includes a complete occupational history with information on extent of past exposures (including environmental sampling data, if possible) and use of protective equipment. Surrogates for worker exposure, in the absence of environmental sampling data, include:

- records of drugs and quantities handled,
- hours spent handling these drugs per week, and
- number of preparations/administrations per week.

The physical examination should be complete, but the skin, mucous membranes, cardiopulmonary, lymphatic system, and liver should be emphasized. An evaluation for respirator use must be performed in accordance with 29 CFR 1910.134, if the employee will wear a respirator. The laboratory assessment may include a complete blood count with differential, liver function tests, blood urea nitrogen, creatinine, and a urine dipstick. Other aspects of the physical and laboratory evaluation should be guided by known toxicities of the HD of exposure. Due to poor reproducibility, inter-individual variability, and lack of prognostic value regarding disease development, no biological monitoring tests (e.g., genotoxic markers) are currently recommended for routine use in employee surveillance. Biological marker testing should be performed only within the context of a research protocol.

## **B. Periodic Medical Examinations**

Recognized occupational medicine experts in the HD area recommend these exams to update the employee's medical, reproductive, and exposure histories. They are recommended on a yearly basis or every 2 to 3 years. The interval between exams is a function of the opportunity for exposure, duration of exposure, and possibly the age of the worker at the discretion of the occupational medicine physician, guided by the worker's history. Careful documentation of an individual's routine exposure and any acute accidental exposures are made. The physical examination and laboratory studies follow the format outlined in the pre-placement examination.<sup>64</sup>

### **C. Post Exposure Examinations**

Postexposure evaluation is tailored to the type of exposure (e.g., spills or needle sticks from syringes containing HDs). An assessment of the extent of exposure is made and included in the confidential database (discussed below) and in an incident report. The physical examination focuses on the involved area as well as other organ systems commonly affected (i.e., for CDs the skin and mucous membranes; for aerosolized HDs the pulmonary system). Treatment and laboratory studies follow as indicated and should be guided by emergency protocols.

### **D. Exit Examinations**

The exit examination completes the information on the employee's medical, reproductive and exposure histories. Examination and laboratory evaluation should be guided by the individual's history of exposures and follow the outline of the periodic evaluation.

### **E. Exposure-Health Outcome Linkage**

Exposure assessment of all employees who have worked with HDs is important, and the maintenance of records is required by 29 CFR 1910.1020. The use of previously outlined exposure surrogates is acceptable, although actual environmental or employee monitoring data is preferable. A SDS can serve as an exposure record. Details of the use of personal protective equipment and engineering controls present should be included. A confidential database should be maintained with information regarding the individual's medical and reproductive history, with linkage to exposure information to facilitate epidemiologic review.

### **F. Reproductive Issues**

The examining physician should consider the reproductive status of employees and inform them regarding relevant reproductive issues. The reproductive toxicity of hazardous drugs should be carefully explained to all workers who will be exposed to these chemicals, and is required for those chemicals covered by the HCS. Unfortunately, no information is available regarding the reproductive risks of HD handling with the current use of BSCs and PPE. However, as discussed earlier, both spontaneous abortion and congenital malformation excesses have been documented among workers handling some of these drugs without currently recommended engineering controls and precautions. The facility should have a policy regarding reproductive toxicity of HDs and worker exposure in male and female employees and should follow that policy.

## **VII. Hazard Communication**

*This Section is for informational purposes only and is not a substitute for the requirements of the Hazard Communication Standard.*

### **A. Discussion**

The Hazard Communication Standard (HCS),<sup>107</sup> is applicable to some drugs. It defines a hazardous chemical as any chemical which is a physical hazard or a health hazard.

Physical hazard refers to characteristics such as combustibility or reactivity. A health hazard is defined as a chemical for which there is statistically significant evidence based on at least one study conducted in accordance with established scientific principles that acute or chronic health effects may occur in exposed employees. Appendices A and B of the HCS outline the criteria used to determine whether an agent is hazardous.

According to HCS Appendix A, agents with any of the following characteristics would be considered hazardous:

- Carcinogens,
- Corrosives,
- Toxic or highly toxic (defined on the basis of median lethal doses),
- Irritants,
- Sensitizers, or
- Target organ effectors, including reproductive toxins, hepatotoxins, nephrotoxins, neurotoxins, agents which act on the hematopoietic system, and agents which damage the lungs, skin, eyes, or mucous membranes.

Both human and animal data are to be used in this determination. HCS Appendix C lists sources of toxicity information.

As a result of the February 21, 1990, Supreme Court decision,<sup>21</sup> all provisions of the Hazard Communication Standard [29 CFR 1910. 1200]<sup>107</sup> are now in effect for all industrial segments. This includes the coverage of drugs and pharmaceuticals in the nonmanufacturing sector. On February 9, 1994, OSHA issued a revised Hazard Communication Final Rule with technical clarification regarding drugs and pharmaceutical agents.

The Hazard Communication Standard (HCS) requires that drugs posing a health hazard (with the exception of those in solid, final form for direct administration to the patient, i.e., tablets or pills) be included on lists of hazardous chemicals to which employees are exposed.<sup>107</sup> Their storage and use locations can be confirmed by reviewing purchasing office records of currently used and past used agents such as those in Appendix VI:2-1. Employee exposure records, including

workplace monitoring, biological monitoring, and SDSs as well as employee medical records related to drugs posing a health hazard must be maintained and access to them provided to employees in accordance with 29 CFR 1910.1020. Training required under the HCS should include all employees potentially exposed to these agents, not only health care professional staff but also physical plant, maintenance, or support staff.

SDSs are required to be prepared and transmitted with the initial shipment of all hazardous chemicals including covered drugs and pharmaceutical products. This excludes drugs defined by the Federal Food, Drug, and Cosmetic Act which are in solid, final form for direct administration to the patient (e.g., tablets, pills, or capsules) or which are packaged for sale to consumers in a retail establishment. Package inserts and the *Physician's Desk Reference* are not acceptable in lieu of requirements of SDSs under the Standard. Items mandated by the Standard will use the term *shall* instead of *should*.

## **B. Written Hazard Communication Program**

Employers shall develop, implement, and maintain at the workplace a written hazard communication program for employees handling or otherwise exposed to chemicals, including drugs that represent a health hazard to employees. The written program will describe how the criteria specified in the Standard concerning labels and other forms of warning, SDSs, and employee information and training will be met.

This also includes the following:

- a list of the covered hazardous drugs known to be present using an identity that is referenced on the appropriate SDS,
- the methods the employer will use to inform employees of the hazards of nonroutine tasks in their work areas,
- and the methods the employer will use to inform employees of other employers of hazards at the work site.

The employer shall make the written hazard communication program available, upon request, to employees, their designated representatives, and the Assistant Secretary of OSHA in accordance with requirements of the HCS.

## **C. Safety Data Sheets (SDS's)**

In accordance with requirements in the Hazard Communication Standard, the employer must maintain SDSs accessible to employees for all covered HDs used in the hospital. Specifics regarding SDS content are contained in the Standard. Essential information includes: health hazards, primary exposure routes, carcinogenic evaluations, acute exposure treatment, chemical inactivators, solubility, stability, volatility, PPE required, and spill procedures for each covered HD. SDSs shall also be made readily available upon request to employees, their designated representatives, or the Assistant Secretary of OSHA.

## **VIII. Training and Information Dissemination**

### **A. Discussion**

In compliance with the Hazard Communication Standard, all personnel involved in any aspect of the handling of covered HDs (physicians, nurses, pharmacists, housekeepers, employees involved in receiving, transport or storage) must receive information and training to appraise them of the hazards of HDs present in the work area.<sup>71</sup> Such information should be provided at the time of an employee's initial assignment to a work area where HDs are present and prior to assignments involving new hazards. The employer should provide annual refresher information and training.

The National Study Commission on Cytotoxic Exposure has recommended that knowledge and competence of personnel be evaluated after the first orientation or training session, and then yearly, or more often if a need is perceived.<sup>71</sup> Evaluation may involve direct observation of an individual's performance on the job. In addition, non-HD solutions should be used for evaluation of preparation technique; quinine, which will fluoresce under ultraviolet light, provides an easy mechanism for evaluation of technique.

### **B. Employee Information**

Employees must be informed of the requirements of the Hazard Communication Standard, 29 CFR 1910.1200:

- any operation/procedure in their work area where drugs that present a hazard are present, and
- the location and availability of the written hazard communication program.

In addition, they should be informed regarding:

- any operations or procedure in their work area where other HDs are present, and
- the location and availability of any other plan regarding HDs.

### **C. Employee Training**

Employee training must include at least:

- Methods and observations that may be used to detect the presence or release of a HCS-covered hazardous drug in the work area (such as monitoring conducted by the employer, continuous monitoring devices, visual appearance or odor of covered HDs being released, etc.),
- The physical and health hazards of the covered HDs in the work area,
- The measures employees can take to protect themselves from these hazards. This includes specific procedures that the employer has implemented to protect the employees from exposure to such drugs, such as identification of covered drugs and those to be

handled as hazardous, appropriate work practices, emergency procedures (for spills or employee exposure), and

- Personal protective equipment, and the details of the hazard communication program developed by the employer, including an explanation of the labeling system and the SDS, and how employees can obtain and use the appropriate hazard information.

It is essential that workers understand the carcinogenic potential and reproductive hazards of these drugs. Both females and males should understand the importance of avoiding exposure, especially early in pregnancy, so the drugs. Both females and males should understand the importance of avoiding exposure, especially early in pregnancy, so they can make informed decisions about the hazards involved. In addition, the facility's policy regarding reproductive toxicity of HDs should be explained to workers. Updated information should be provided to employees on a regular basis and whenever their jobs involve new hazards. Medical staff and other personnel who are not hospital employees should be informed of hospital policies and of the expectation that they will comply with these policies.

## **IX. Recordkeeping**

Any workplace exposure record created in connection with HD handling shall be kept, transferred, and made available for at least 30 years and medical records shall be kept for the duration of employment plus 30 years in accordance with the Access to Employee Exposure and Medical Records Standard (29 CFR 1910.1020).<sup>108</sup> In addition, sound practice dictates that training records should include the following information:

- Dates of the training sessions,
- Contents or a summary of the training sessions,
- Names and qualifications of the persons conducting the training, and
- Names and job titles of all persons attending the training sessions.

Training records should be maintained for three years from the date on which the training occurred.

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## **APPENDIX VI:2-1 Some Common Drugs Considered Hazardous**

Appendix VI:2-1 is not all-inclusive, should not be construed as complete, and represents an assessment of some, but not all, marketed drugs at a fixed point in time. Appendix VI:2-1 was developed through consultation with institutions that have assembled teams of pharmacists and other health care personnel to determine which drugs should be handled with caution. These teams reviewed product literature and drug information when considering each product.

Sources for this appendix are the "Physicians Desk Reference," Section 10:00 in the *American Hospital Formulary Service Drug Information*,<sup>68</sup> IARC publications (particularly Volume 50),<sup>43</sup> the Johns Hopkins Hospital, and the National Institutes of Health, Clinical Center Nursing Department. No attempt to include investigational drugs was made, but they should be prudently handled as hazardous drugs until adequate information becomes available to exclude them.

Any determination of the hazard status of a drug should be periodically reviewed and updated as new information becomes available. Importantly, new drugs should routinely undergo a hazard assessment.

<b>CHEMICAL/GENERIC NAME</b>	<b>SOURCE*</b>
ALTRETAMINE	C
AMINOGLUTETHIMIDE	A
AZATHIOPRINE	ACE
L-ASPARAGINASE	ABC
BLEOMYCIN	ABC
BUSULFAN	ABC
CARBOPLATIN	ABC
CARMUSTINE	ABC
CHLORAMBUCIL	ABCE
CHLORAMPHENICOL	E
CHLOROTIANISENE	B
CHLOROZOTOCIN	E
CYCLOSPORIN	E
CISPLATIN	ABCE
CYCLOPHOSPHAMIDE	ABCE
CYTARRABINE	ABC
DACARBAZINE	ABC
DACTINOMYCIN	ABC
DAUNORUBICIN	ABC
DIETHYLSTILBESTROL	BE
DOXORUBICIN	ABCE
ESTRADIOL	B
ESTRAMUSTINE	AB
ETHINYL ESTRADIOL	B
ETOPOSIDE	ABC
FLOXURIDINE	AC

CHEMICAL/GENERIC NAME	SOURCE* (Continued)
FLUOROURACIL	ABC
FLUTAMIDE	BC
GANCICLOVIR	AD
HYDROXYUREA	ABC
IDARUBICIN	AC
IFOSFAMIDE	ABC
INTERFERON-A	BC
ISOTRETINOIN	D
LEUPROLIDE	BC
LEVAMISOLE	C
LOMUSTINE	ABCD
MECHLORETHAMINE	BC
MEDROXYPROGESTERONE	B
MEGESTROL	BC
MELPHALAN	ABCE
MERCAPTOPYRINE	ABC
METHOTREXATE	ABC
MITOMYCIN	ABC
MITOTANE	ABC
MITOXANTRONE	ABC
NAFARELIN	C
PIPOBROMAN	C
PLICAMYCIN	BC
PROCARBAZINE	ABCE
RIBAVIRIN	D
STREPTOZOCIN	AC
TAMOXIFEN	BC
TESTOLACTONE	BC
THIOGUANINE	ABC
THIOTEPA	ABC
URACIL MUSTARD	ACE
VIDARABINE	D
VINBLASTINE	ABC
VINCRISTINE	ABC
ZIDOVUDINE	D

\*Sources

- A - The National Institutes of Health, Clinical Center Nursing Department
- B - Antineoplastic drugs in the [italicize the following text name] Physicians' Desk Reference
- C - American Hospital Formulary, Antineoplastics
- D - Johns Hopkins Hospital
- E - International Agency for Research on Cancer

## **APPENDIX VI:2-2 Some Aerosolized Drugs**

### **RIBAVIRIN**

Ribavirin is a synthetic nucleoside with antiviral activity against respiratory syncytial virus (RSV). It appears to restrict synthesis of viral proteins by interfering with mRNA production, but the exact mechanism of action remains unknown.<sup>34</sup> It is reconstituted from a lyophilized powder for aerosol administration.

Ribavirin is usually administered in the aerosolized form via mask or oxygen tent for 12-18 hours per day for 3 to 7 days. A small particle aerosol generator (SPAG) creates respirable particles of 1.3 micrometer median diameter. Under current practice, excess drug is exhausted into the patient's room, causing additional exposures.

Studies have shown Ribavirin to be teratogenic in rodents and embryolethal in rabbits. Ribavirin induces cell transformation in an in vitro mammalian system (Balb/C 3T3 cell line). In vivo carcinogenicity studies are incomplete.

Human studies on nurses who administer the drug by oxygen tent calculate that the absorbed dose of riba-virin per workshift is 13.5 mg/kg.<sup>31</sup> This estimated dose exceeded 1/100 (the safety factor) of the short term daily dose levels toxic in animal models described above. No symptoms were reported by any health care worker in this study. However, minor pulmonary function abnormalities have been seen among healthy adult volunteers in clinical studies.<sup>12, 18</sup>

### **PENTAMIDINE**

Aerosolized pentamidine isethionate (4,4'-diaminodiphenoxypentane) is FDA approved for the treatment and prophylaxis of pneumonia caused by the protozoan *Pneumocystis carinii*. The exact mode of action is not fully understood; some studies indicate that pentamidine interferes with nuclear metabolism, inhibiting the synthesis of DNA, RNA, phospholipids, and proteins. It possesses two amidine groups and resembles other compounds called electrophiles which form DNA adducts. Pentamidine is administered as an aerosol after being reconstituted from a lyophilized powder.

No studies have been performed to evaluate the potential carcinogenic, mutagenic, or reproductive effects of pentamidine in animals or humans.<sup>63</sup>

Studies among health care workers have demonstrated pentamidine uptake by those personnel who administer the drug. Side effects include coughing, sneezing, mucous membrane irritation, headache, and bronchospasm. Pulmonary function tests have demonstrated transitory decreases in carbon monoxide diffusing capacity (DLCO). However, one respiratory therapist followed for 14 months has not returned to baseline after exposure.<sup>29</sup>