

Compounding Containment Devices: Buyer Be Aware

Eric S. Kastango, RPh, MBA, FASHP

Clinical IQ, LLC, Madison, New Jersey

The risk of occupational exposure to chemicals used in the extemporaneous and batch compounding of human and veterinary oral, topical, ophthalmic, vaginal, rectal, and parenteral products is significant. As pharmacists, we must be concerned about the long-term effects of exposure to drugs such as progesterone, estrogen, testosterone, ganciclovir, fentanyl, and other chemical entities that exert specific metabolic actions. Compounding pharmacists and technicians may be unwittingly exposed to such chemicals because the efficiency of containment devices and the sites in which they are used vary considerably. A recent study¹ has shown that substantial levels of antineoplastic agents compounded in biological safety cabinets (BSCs) were found on various surfaces inside and outside the BSCs in the drug preparation and administration areas. In a study conducted by Hansen and Olsen,² Danish female pharmacy technicians reported significant increases in the incidences of non-melanoma skin cancer and non-Hodgkin's lymphoma. It has been estimated that more than 300,000 pharmacy staff employees who prepare or administer medications and millions of nurses, patients, care partners, and families are exposed to hazardous drugs used in the treatment of cancer and AIDS.³

The facility and operating environment in which sterile and clean pharmacy-prepared products are compounded and containment devices are used must be managed and controlled to ensure that the highest quality sterile products are produced and that maximum containment protection is provided for the operators and the surrounding environment.

Considerations for selecting a containment device to be used in compounding and methods of ensuring that the device functions reliably are presented in this article. Providing protection for operators and the surrounding environment is also addressed. That information can be used before a purchase has been made to evaluate various containment devices and the vendor services (certification and maintenance) required to support them.

The Right Device for the Right Job

P. T. Barnum, the world-famous showman, is often quoted as having said that "A sucker is born every minute." The compounding pharmacist who selects and purchases a containment device that he or she knows little about risks garnering that title.

It is important to "know thy process and products" used during compounding because those factors determine the type of containment device that should be selected. Only a portion of the activities performed in a containment device will require sequestered preparation. Factors such as particle size, outgassing, and misting can greatly affect the performance of containment devices.

Not everything is as it appears. The containment device being considered for purchase may be poorly designed from a function-

al or ergonomic perspective or may even be ineffective in achieving the type of control required (airflow velocity, vacuum or containment control). It is important to select value-added resellers (VARs) and/or manufacturers who want to know which activities will be performed in the containment device before it is sold. To ensure the selection of the right device, the VAR and the buyer should conduct a risk assessment based on the functions to be performed. Genotoxic, carcinogenic, or teratogenic chemicals must be prepared in containment devices different from those used in the preparation of nontoxic substances.

Buyers must be aware of the most current recommendations or guidelines for handling and preparing chemicals used in compounding before they purchase a containment device. Organizations that routinely publish information about containment devices and handling procedures include the American Society of Health-System Pharmacists (ASHP), the Occupational Safety and Health Administration (OSHA), and the National Institute for Occupational Safety and Health (NIOSH). Material safety data sheets (MSDSs), which can be obtained from drug manufacturers, provide the operator with a biological risk assessment of the chemicals used, as well as information about abatement procedures, protective equipment, and protective apparel.

Laboratory Fume Hoods or Source Capture Devices

This equipment is usually used in pharmacies to isolate particles generated when powders are weighed. Fume hoods were originally designed to capture, contain, and vent chemical fumes and vapors from the environment. They do not protect the compounded product from viable or nonviable contamination because room air is drawn into and through the critical work areas of these devices. The capabilities of fume hoods during the extemporaneous compounding of powders are not well defined, and no testing standards exist. According to Hank Rahe,⁴ an expert in conventional and advanced aseptic processing, certification and testing experts agree that no good methods exist for determining whether fume hoods or source capture devices function properly for a particular application. These devices may create a false sense of security. As a result, the operator, the surrounding environment, and others working in that environment may be contaminated with hazardous airborne particles. Because progesterone is considered a carcinogen, that danger is present during the preparation of bioidentical hormone replacement formulations.⁵

Clean Benches

Clean benches (horizontal laminar airflow hoods) create controlled environmental conditions in which the number of viable and nonviable particles is controlled through the use of a high-efficiency particulate air (HEPA) filter. HEPA-filtered air moves horizontally. Because the operator sits within the stream of HEPA-filtered air, this containment device should not be used when toxic or biohazardous chemicals must be handled.

Types of Containment Devices.

Laboratory fume hoods or source capture devices
 (Laminar flow) clean benches
 Controlled atmosphere glove boxes
 Ventilated glove boxes
 Biological safety cabinets

Biological Safety Cabinets

In biological safety cabinets (BSCs), which are containment devices similar to clean benches, HEPA filters are used to create controlled environmental conditions. BSCs, however, are designed to protect the operator and the environment from exposure to toxic or biohazardous chemicals. Biological safety cabinets are classified as class I, II, or III.

Class I BSCs

These containment devices are ventilated cabinets that protect personnel and the environment. They do not protect the product within the cabinet. Class I BSCs are similar to fume hoods; however, a HEPA filter at the exhaust outlet may channel exhaust back into the work area or into an exhaust-duct system.

Class II BSCs

These ventilated cabinets, which are classified as class I or II, protect personnel, products, and the environment from exposure to toxic chemicals. Type A and type B are the two types of class II BSCs. All class II cabinets have (at a minimum) an open front with an inward airflow, HEPA-filtered down-flowing air, and a HEPA filter at the exhaust outlet that may channel exhaust back into the work area or into an exhaust-duct system. Type A and type B cabinets differ as follows^{1,6}:

- A class II A cabinet has a minimum calculated average face in-flow velocity of 75 feet per minute (fpm), positive-pressure "contaminated" ducts (ducts through which recirculated air from the work area is channeled) and plenums
- A class II B2 cabinet has a minimum calculated average face in-flow velocity of 100 fpm and 30% air recirculation from the cabinet plenum into the work area. All contaminated ducts and cabinet plenums are under negative pressure.
- A class II B3 cabinet has a minimum calculated average face in-flow velocity of 100 fpm, channels all exhaust air to the outside, and has either negative-pressure contaminated ducts or is surrounded by negative-pressure contaminated ducts and plenums.

Class III BSCs

These totally enclosed ventilated cabinets are containment devices with a gas-tight construction. They are similar in design to

In-cap



Minicap
100



SCHAEFER
TECHNOLOGIES, INC.

Schaefer sets the Gold Standard in Capsule Filling and Isolation Technology



Enguard

For More Information Call:
(800) 435-7174

e-mail: kjs@indy.net www.schaefer-technologies.com

Other Standards for Fume Hoods.

One of the biggest challenges facing buyers of fume hoods or source capture systems is the standard by which those devices should be certified to ensure that they are operating properly. Because there are no testing standards for containment devices, the prospective buyer should review the current literature to identify technical and performance standards for fume hoods. Examples of a standard include University of Kentucky's (UK) guideline.

The guidelines listed below should be used by those who are operating a fume hood or a source capture system without knowing the range of function of the equipment and the levels of containment and protection provided. Although marker powder could be used to determine the capture capabilities of a fume hood or a source capture system, the physical characteristics (particle size, structure, flow properties, etc) of the powder and those of the chemicals routinely used in the device would have to be the same. Smoke, when used to study the airflow dynamics of the products used routinely in containment devices, does not emulate the airflow characteristics of powders.⁴ Testing verifies the effectiveness of the containment device objectively rather than subjectively.

UK Design Guidelines & Technical Standards Committee for Fume Hoods on June 18, 1998¹²

GENERAL

Fume hood systems shall be designed to protect laboratory workers and to ensure that hazardous chemical vapors originating from laboratory operations shall not be recirculated. The use of variable air volume systems is preferred. Additional requirements include:

- Designed to provide 100 linear feet per minute face velocity at a height of twelve inches.
- Maintain a set point within five percent within one second of any change in fume hood sash position, or changes in the exhaust and/or supply systems; except in those cases where the existing building's HVAC systems are not capable of complying with this requirement.
- Provide flow detectors/alarms.

FUME HOOD LOCATION

- Fume hoods must not be located adjacent to a single means of access to an exit or in high traffic areas.
- Locate away from doors, operable windows, and in general located to minimize cross drafts and air disruption.
- Supply air diffusers air jet velocity shall be less than half (preferably less than one third) of capture velocity of the exhaust hood.

FUME HOOD EXHAUST

- Fume hood exhaust discharges must be designed to minimize air re-entry, take into account aesthetic appearance, and minimize exposures to maintenance workers.

- Locate fans on roof or in a separate room (penthouse) that is maintained at a negative pressure to the rest of the building and is well ventilated.
- A motion/light sensor may be utilized to lower exhaust rate to 60 linear feet per minute when fume hood is not in use.
- Exhaust system must be constructed entirely of noncombustible materials; have all joints and connections sealed; and should use materials resistant to acids, bases, solvents and corrosive gases.

SOUND LEVELS

- Fume hood exhaust systems must be designed to minimize sound level problems.
- Designed to keep noise levels less than 68 db(A) one foot in front of hood face with hoods running.

RECIRCULATING FUME HOODS

- Ductless hoods which filter air (through HEPA or charcoal filters) [and] then discharge the filtered air back into the laboratory may not be used without approval of the directors of Hazardous Materials Management and Occupational Health and Safety.

AIR CLEANING DEVICES

- Air cleaning devices are not generally required for laboratory fume hoods, and may not be used without approval of the directors of Hazardous Materials Management and Occupational Health & Safety departments.

Used by permission from University of Kentucky, EH&S, Occupational Health and Safety.

For general questions, concerns and comments, contact Lee Poore, Laboratory Safety Specialist, 252 East Maxwell Street, Lexington, KY 40506-0314. Phone: (859) 257-2924; Fax: (859) 257-8787.

glove boxes because all tasks are performed by an operator wearing rubber gloves that are attached to the cabinet. The BSC is maintained under a negative air pressure of at least 0.5 inches wg (water gauge). The exhaust air undergoes double and then single HEPA filtration and subsequent incineration. Class III BSCs are used when extremely toxic or infectious agents such as hemorrhagic fever viruses are handled.^{1,7}

Critical Selection Criteria

The safety provided by a containment device and its cost and size should be carefully considered before the device is purchased.

Safety

The type of device selected should depend on the type of protection required and the safety risks associated with handling the chemicals compounded inside the device. Understanding the de-

sign and engineering of the various containment devices is important. Many chemicals produce fine particles, gasses, or vapors when they are handled or during compounding. The three types of protection that containment units provide are product protection only; personnel and environmental protection; or product, personnel, and environmental protection.⁶

The type of exhaust system needed to ensure the safety of personnel and to meet applicable local and state environmental codes should be considered. For example, cyclophosphamide, a commonly used antineoplastic agent, has a very low vapor pressure. Vaporization, which occurs during routine compounding, reduces the size of the cyclophosphamide molecule enough to render HEPA filtration ineffective. As a result, vaporized cyclophosphamide escapes freely from the containment environment. Particles of fluorouracil, cyclophosphamide, and ifosfamide have been absorbed by operators and other personnel in work areas adjacent to compounding sites in six cancer treatment centers in Canada and the United States; however, it was not clear whether the BSCs were vented to the outside in those cases.^{1,7} The following three factors contribute to the contamination of operators and the environment⁸:

- **Process-related issues.** Excessive movement of materials and the operator in and out of the BSC
- **Aseptic technique.** Poor operator technique in preventing spills of antineoplastic drugs and the subsequent contamination of product containers
- **Training.** Failure to train employees adequately in the safe handling of antineoplastic agents and the proper operation of containment devices

The American Journal of Health-System Pharmacy study⁹ indicates that many containment devices do not protect the operator and the environment from contamination. As a result, the National Institute for Occupational Safety and Health (NIOSH), through its National Occupational Research Agenda (NORA) initiative, has formed a working group to identify short-term and long-term methods of reducing occupational exposure to antineoplastic agents. Issues addressed by the working group include engineering controls (PhaSeal, Carmel Pharma, Inc, Shelton, Connecticut), work practice controls (including administrative controls such as employee training and material handling procedures), and personal protective equipment, such as gloves and respirators. Recommendations from the NIOSH working group that address those issues will be published at the end of the 2001 fiscal year.

Venting

Venting BSCs to the outside may not be the answer to the problem of environmental or operator contamination. Improper venting may inadvertently channel toxic substances back into the building via the air-handling system.⁷ The importance of working with trained and qualified contractors who can properly install an external venting system cannot be overemphasized.

Cost

The total cost of a containment device must include the expense of the cabinet, a remote blower, and an exhaust system that includes ductwork and alarms. Other costs include the expense of the initial certification of the containment device (which may be negotiated as part of the sale price) and the operating and maintenance

cost of electrical power and air conditioning. Electrical motors in some containment devices generate a significant amount of heat, which may tax existing HVAC (heating, ventilation, and air conditioning) resources. Annual maintenance costs must include the expense of recertification and the replacement of prefilters. HEPA filters must be replaced when the differential pressure across the filter is greater than that specified in the design requirements for the filter. Properly installed HEPA filters have a service life of approximately 8 to 10 years.¹⁰

Size

Containment devices are available in many shapes and sizes that range from 2 to 8 feet in width and 3 to 8 feet in length. Some manufacturers will customize the size of the containment device to meet specific needs at a substantial cost. The size should enable the non-cluttered placement of all materials in the work space.

Operating Standards

The buyer who purchases a containment device from a VAR or a manufacturer should verify that the device is working properly and can be operated according to industry standards. The critical operating requirements for each device should be specified in the manufacturer's operating and maintenance manuals. The successful testing or verification of those parameters indicates that the device meets the manufacturer's specifications and specific industry standards (ie, NSF International Standard Number 49 [NSF 49], etc). NSF International, which is a nonpartisan, third-party, independent organization, develops national standards and third-party assessment services that represent industry, the regulatory community, and the public.¹¹ A qualified certification vendor should be the only individual permitted to perform and document the results of certification.

NSF 49

At the request of the Centers for Disease Control and Prevention (CDC), the National Institute of Health (NIH), and the National Cancer Institute (NCI), NSF International was commissioned to develop a national standard (NSF 49) that defines the minimal materials in, the design and construction of, and performance requirements for class II biohazard cabinets; the quality control tests that the manufacturer must perform on each unit; and the tests for proper function that should be performed in the field. NSF International, an independent, not-for-profit organization, completed the implementation of the Biohazard Cabinetry Certification Program in 1993.

A BSC that is certified as meeting NSF 49 requirements must produce satisfactory results in three biological challenge tests: two personal protection tests (one that measures the amount of bacterial spores that escape from the cabinet's work area into the environment and one that measures the amount of bacterial spores entering the work area from the outside environment) and a cross-contamination protection test, which measures how far bacterial spores generated in the work area drift across that area.⁶

To ensure that a BSC can protect the operator, the product, and the environment even if the manufacturer's recommended down-flow and inflow velocities are achieved, performance zone tests (additional biological challenges) are performed at various operating velocities. The operating standards surrounding Federal Standard

Table 1. Performance Tests for Biological Safety Cabinets.

Performance Factor	Biosafety Cabinet		
	Class I	Class II	Class III
Primary containment			
Cabinet integrity	N/A	A	A
HEPA filter leak	B	B	B
Downflow velocity profile	A	B	B
Negative pressure/ ventilation rate	C	A	B
Airflow smoke patterns	B	B	D/E
Alarms and interlocks	F, G	F, G	B
Electrical safety			
Electrical leakage, etc	D, G	D, G	D, G
Ground fault interrupter	G	G	G
Other			
Lighting intensity	D	D	D
Ultraviolet light intensity	D, F	D, F	D, F
Noise level	D	D	D
Vibration	D	D	D
N/A, not applicable	C, if used with gloves		
A, required for proper certification if the cabinet is new or has been moved or if panels have been removed for maintenance	D, optional at the discretion of the user		
HEPA, high-energy particulate air (filter)	E, used to determine air distribution within cabinet for clean-to-dirty procedures		
B, required during certification	F, if present		
	G, encouraged for electrical safety		
Source: Richmond JY, McKinney RW. <i>Primary Containment for Biohazards: Selection, Installation and Use of Biological Safety Cabinets</i> . Washington, DC: US Government Printing Office; 1995.			

209E and the ISO 14644-X series were discussed in great detail in Volume 5, Number 3 of *IJPC* in the article titled "Pharmacy Clean-room Project Management Considerations: An Experience-Based Perspective."

Certification

A consistent performance is necessary if a containment device is to minimize or prevent contamination to the operator, the product, and the environment. To ensure the proper operating performance of a device, routine certification should be performed at the time of installation, every 6 months, and whenever the device is serviced or moved. NSF 49 is used to evaluate BSCs. The recommended tests for BSCs are shown in Table 1.¹³

Treat the Cause and Not the Symptom

Being aware of the potential danger of unintended occupational exposure to antineoplastic or other chemicals is essential in compounding pharmacy. Training and proficiency in aseptic technique can reduce the operator's exposure to contaminants. Compounding pharmacists must read the current literature on ensuring adequate protection from occupational hazards; valuable information

on that topic will be provided on the NIOSH Website later this year. Evaluate the precautionary activities and processes in your pharmacy. Are they adequate? Do the containment devices used to prepare preparations protect the operator and the surrounding work area from contamination? If you have containment devices that have not been certified within the past 6 months, *have them certified*. If a new containment device is needed, evaluate available models carefully before purchase. Ask VARs or manufacturers for the results of objective testing procedures performed by a trained and qualified third-party certification company. *Trust, but verify!*

Acknowledgment

The author thanks Kate Douglass, CCNS, MS, CRNI, and Sam DeMarco, BSME, MBA, for providing technical information used to write this article.

References

- Connor TH, Anderson RW, Sessink PA, et al. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health Syst Pharm* 1999;56:1427-1431.
- Hansen J, Olsen JH. Cancer morbidity among Danish female pharmacy technicians. *Scand J Work Environ Health* 1994;20:22-26.
- Department of Health and Human Services. Hazardous drug safe handling: Identifying problems; building solutions. Paper presented at: NIOSH Working Group Meeting; December 13, 2000; Washington, DC.
- Rahe H. Containment device misuse. *CleanRooms* 2000;14:12.
- Progesterone [material safety data sheet]. New Brunswick, NJ: Spectrum Chemical Mfg Company; 1993. Available at: <http://hazard.com/msds2/f/93/chxhl.html>. Accessed May 3, 2001.
- Personnel & Product Protection: A Guide to Biosafety Enclosures*. Kansas City, MO: Labconco Corporation; 1993.
- Rahe H. A call to arms. *CleanRooms* 1999. Available at: http://cr.pennnet.com/Articles/Article_Display.cfm?Section=Archives&Subsection=Display&ARTICLE_ID=42633. Accessed May 3, 2001.
- Rahe H. Life science: All of the above. *CleanRooms* 1999;December. Available at: http://cr.pennnet.com/Articles/Article_Display.cfm?Section=Archives&Subsection=Display&ARTICLE_ID=54451. Accessed May 3, 2001.
- Connor TH, Anderson RW, Sessink PA, et al. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health Syst Pharm* 1999;56:1427-1431.
- Matthews RA. Half-truths can be believable. *CleanRooms* 2000;March:78. Available at: http://cr.pennwellnet.com/Articles/Article_Display.cfm?Section=Archives&Subsection=Display&ARTICLE_ID=66452&KEYWORD=Debunking%20the%20Myths. Accessed December 26, 2000.
- NSF International Website. 2001. Available at: <http://www.nsf.org>. Accessed May 3, 2001.
- University of Kentucky. *Technical Standards and Performance Standards: Fume Hoods*. Lexington, KY: UK Design Guidelines & Technical Standards Committee; 1998. Available at: <http://www.uky.edu/FiscalAffairs/Environmental/ohs/fumehood.html>. Accessed on May 3, 2001.
- Richmond JY, McKinney RW, eds. *Primary Containment for Biohazards: Selection, Installation and Use of Biological Safety Cabinets*. September 1995. Richmond, JY, McKinney, RW (ed). U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention and National Institutes of Health. Available at: <http://www.niehs.nih.gov/odhsb/biosafe/bsc/table3.htm> Accessed May 2, 2001.

Address correspondence to: Eric S. Kastango, RPh, MBA, FASHP, Clinical IQ, LLC, 21 Madison Plaza, Suite 149, Madison, NJ 07940-1410. E-mail: ekastango@clinicaliq.com ■