



# COMMONWEALTH OF VIRGINIA

## Meeting of the Board of Pharmacy

Perimeter Center, 9960 Mayland Dr., Second Floor  
Richmond, Virginia 23230

(804) 367-4456 (Tel)  
(804) 527-4472 (Fax)

### Tentative Agenda of Meeting Regulation Committee for Automated Counting Devices, Automated Dispensing Devices, and Definition of "Low Volume"

*November 29, 2011*

**1:00pm – 5:00pm**

<u>TOPIC</u>	<u>PAGE(S)</u>
<b>Call to Order:</b> Ellen Shinaberry, Committee Chairman <ul style="list-style-type: none"><li>• Welcome and Introductions</li><li>• Reading of emergency evacuation script</li><li>• Approval of Agenda</li></ul>	
<b>Call for public comment:</b> The Board will not receive comment on any regulation process for which a public comment period has closed or any pending disciplinary matters. The Board will receive comments on specific topics on this agenda at the time the matter is taken up by the Board.	
<b>Discuss current "run dry" requirement for automated counting devices in Regulation 18VAC110-20-355C</b>	<b>1-5</b>
<b>Identify possible changes to Regulation 18VAC110-20-490 regarding automated dispensing devices</b>	<b>6-32</b>
<b>Discuss need for "low volume" definition</b>	<b>33-74</b>

**Adjourn:** The committee will adjourn at approximately 5pm.

**\*The Committee will have a working lunch at 1pm.**

# Run Dry Requirement for Automated Counting Devices

- Review "Run Dry" Requirement for Automated Counting Devices:

Ms. Juran reported that Delegate Chris Jones had indicated in a recent conversation with her that the "run dry" requirement in Regulation 18VAC 110-20-355 may currently be overly burdensome. He explained to Ms. Juran that there is an increasing trend to use automated counting devices to more securely store certain slow-moving drugs which do not inherently empty from the bin every sixty days. Ms. Juran stated she reviewed the other states' regulations for automated counting devices and none had a "run dry" requirement. Alan Friedman representing Kaiser Permanente addressed the Board with his concerns for the regulation. He explained that current counting devices rely on gravity to empty the device to ensure the "first drug in" is the "first drug out", unlike the baker cells used in past when the "run dry" requirement was put in place. He believes the "run dry" requirement is no longer necessary and the Board should consider either eliminating the requirement or requiring an annual "run dry".

**Motion:**

**The Board voted unanimously to refer the review of the "run dry" requirement in Regulation 18VAC 110-20-355 to the regulation committee and for it to collect further information for consideration by the Board. (motion by Munden, second by Rhodes)**

**18VAC110-20-355. Pharmacy repackaging of drug; records required; labeling requirements.**

C. Pharmacies using automated counting devices or dispensers in which drugs are removed from manufacturer's original packaging and placed in bulk bins shall comply with the following requirements:

1. A bin filling record shall be maintained, manually or in a computerized record for a period of one year from the date of filling from which information can be readily retrieved, for each bin including:

a. The drug name and strength, if any;

b. The name of the manufacturer or distributor;

c. Manufacturer's control or lot number(s) and expiration date for all lots placed into the bin at the time of filling;

d. Any assigned lot number;

e. An expiration date determined according to USP guidelines for repackaging;

f. The date of filling; and

g. The pharmacist's initials verifying the accuracy of the process.

2. If more than one lot is added to a bin at the same time, the lot which expires first shall be used to determine the expiration date if shorter than a calculated date based on USP guidelines.

3. Each bin shall be labeled in such a manner as to cross-reference the information on the filling record with the correct expiration date.

4. If only one lot is added to a bin at one time, but a subsequent lot may be added before the first has cleared, the automated device shall be constructed to reasonably dispense the first lot before the second lot is dispensed, the expiration date on the bin's label shall reflect the expiration date assigned to the earlier lot, and the bin shall be allowed to "run dry" where all product is completely removed prior to filling at least once every 60 days with a record made of the run dry dates.

## RESEARCH - "Run Dry" Requirement

- Surveyed inspectors to determine types of automated counting devices seen in practice – Scriptpro, Parata, Innovation, and Yuyama.

### ScriptPro

- Technology resembles a rectangle with an agitator at one end that spins and kicks tablets out in a more horizontal direction, unlike gravity-based that runs top to bottom
- Launched first device around 1996
- Spoke with Derrick Cunningham at Scriptpro & he stated:
  - no current technology could guarantee first in, first out
  - devices allows for scanning stock bottle and manual entry to lot number and expiration date
  - has ability to create a cell run dry report and can set reminder per state requirement or company policy

### Parata

- launched approximately 2003
- uses air-compressed technology
- has not returned Board's call; f/u email sent

### Innovation Smartcabinet

- launched approximately in 2002
- has not returned Board's call; f/u email sent

### Yuyama

- has not returned Board's call; f/u email sent

### Kirby Lester

- spoke with Mike Stotz
  - launched in January 2010
  - no clients currently in Virginia; closest clients in DC, SC, GA, NY, and NJ
  - pills fall into vertical slots and spin around, gravity system, pills move in a downward direction and forcibly ejected
  - did not believe any current technology could assure first in, first out but believed a top to bottom direction flow could improve chances

A search of NAPLAW did not reveal any other states with a "run dry" requirement, however, not all states allow the mixing of lot numbers.

9/20/11- Alan Friedman with Kaiser Permanente recommended the Board either eliminate the requirement or amend to require run dry annually.

11/18/11 – Caroline Juran spoke with Delegate Chris Jones who believes it is reasonable to at least extend the run dry requirement to every 6 months.

**Possible Discussion Questions:**

- Does current technology assure first in, first out?
- Does the concern for expired tablets inadvertently staying in the device bin longer than expected remain?
- Is it reasonable to believe that the bin will inherently run dry within 6 months or 12 months and therefore, lessen the currently perceived burden for manually emptying the bin of slow-movers?

**Possible Options for Committee:**

- Recommend to full board that no change to the current regulation is necessary.
- Recommend to full board to extend allowance for performing a “run dry” to every 6 months or some other period of time when individual bin of automated counting device contains mixed lots.
- Recommend to full board to eliminate requirement for performing a “run dry” when individual bin of automated counting device contains mixed lots.

# Automated Dispensing Devices



# COMMONWEALTH OF VIRGINIA

## Board of Health Professions

9960 Mayland Drive, Suite 300  
Richmond, Virginia 23233-1463

(804) 367-4603 (Tel)  
(804) 527-4466 (Fax)

### Petition for Rule-making

*The Code of Virginia (§ 2.2-4007) and the Public Participation Guidelines of this board require a person who wishes to petition the board to develop a new regulation or amend an existing regulation to provide certain information. Within 14 days of receiving a valid petition, the board will notify the petitioner and send a notice to the Register of Regulations identifying the petitioner, the nature of the request and the plan for responding to the petition. Following publication of the petition in the Register, a 21-day comment period will begin to allow written comment on the petition. Within 90 days after the comment period, the board will issue a written decision on the petition.*

**Please provide the information requested below. (Print or Type)**

**Petitioner's full name (Last, First, Middle initial, Suffix.)**  
Fuller, Courtney M.

**Street Address**  
3008 Rugby Road

**Area Code and Telephone Number**  
804-358-9577

**City**  
Richmond

**State**  
VA

**Zip Code**  
23221

**Email Address (optional)**  
[Courtney.fuller@hcahealthcare.com](mailto:Courtney.fuller@hcahealthcare.com)

**Fax (optional)**

### Respond to the following questions:

1. What regulation are you petitioning the board to amend? Please state the title of the regulation and the section/sections you want the board to consider amending.

18VAC110-20-490 – Automated devices for dispensing and administration of drugs.

"5. Automated dispensing devices shall be inspected monthly by pharmacy personnel to verify proper storage, proper location of drugs within the device, expiration dates, the security of drugs and validity of access codes."

2. Please summarize the substance of the change you are requesting and state the rationale or purpose for the new or amended rule. Propose an amended rule allowing for a complete inspection of automated devices under the above mentioned regulation to be waived under certain circumstances as follows:

- The automated dispensing device is capable and is set to automatically identify and isolate the location of each drug within the device by barcode identification, thereby automatically verifying proper location. A report can be provided verifying such settings.
- Proper storage is verified electronically by devices that are capable of continuous temperature tracking of refrigerated storage, with documented temperature ranges, variance, and resolution.
- Expiration dates are automatically tracked by automated devices that are equipped with such capability, eliminating the need to access each individual location each month for manual date auditing. Proactive reporting allows for replacement of expiring products prior to their expiry.
- Security of drugs is automatically verified by electronic detection of cabinet, drawer, and pocket malfunctions and failures and is a continuous process. These are reviewed and corrected as they occur in order for the device to operate; the default in the event of such failures is to lock out any further operation. There are reports available to review mechanical errors related to such errors.
- Access codes may be verified by a "BioID" system utilizing fingerprint as the "pass code" after initial log-on in order to eliminate sharing or theft of pass codes. BioID can automatically be verified in the system settings as a default.

Automation has been designed and updated to improve drug storage, security, and safety, while streamlining work processes and increasing efficiencies. The above stated advancements in technology easily and automatically accommodate these currently manual processes.

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3. State the legal authority of the board to take the action requested. In general, the legal authority for the adoption of regulations by the board is found in § 54.1-2400 of the Code of Virginia. If there is other legal authority for promulgation of a regulation, please provide that Code reference.

Signature:  
Courtney M. Fuller

16 May 2011

Date:



# COMMONWEALTH OF VIRGINIA

## Board of Pharmacy

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**Please provide the information requested below. (Print or Type)**

**Petitioner's full name (Last, First, Middle initial, Suffix,)**  
Dunavant, Karen L.

**Street Address**  
10705 Burr Oak Way

**Area Code and Telephone Number**  
703-250-5236

**City**  
Burke

**State**  
VA

**Zip Code**  
22015

**Email Address (optional)**  
[Karen.dunavant@hcahealthcare.com](mailto:Karen.dunavant@hcahealthcare.com)

**Fax (optional)**

**Respond to the following questions:**

1. What regulation are you petitioning the board to amend? Please state the title of the regulation and the section/sections you want the board to consider amending.

18VAC110-20-490 Automated devices for dispensing and administration of drugs  
Section 5

2. Please summarize the substance of the change you are requesting and state the rationale or purpose for the new or amended rule. Please consider changing the audit process and/or parameters decrease the amount of time required to comply with monthly controlled substance audits. Section 5 should allow for hospitals with access to software that analyzes automated dispensing machine transactions (examples: RxAuditor, Pandora, etc) to bypass parts of the manual reconciliation process. Hospitals would still need to manually review overrides to ensure there was a doctor's order or any machine that was not on Profile mode (where doctor's orders automatically cross from the hospital's clinical system into the Automated Dispensing Machine). Utilizing RxAuditor reports - the hospital was able to identify 4 possible diverters off of 1 report covering a month's transactions. Utilizing the method set forward in the regulations, these 4 possible diverters would not have been identified as quickly, because the audit only covers 24 hours and 3 of the employees were part-time/prn. The current process set forth by the regulation requires about 48 man-hours every month with little or no result. The RxAuditor reports quickly identified people outside of the norm compared to their peers on the same nursing unit - the narrowed investigations still took time (about 8 hours per employee or 32 man-hours) but the results speak for themselves.

3. State the legal authority of the board to take the action requested. In general, the legal authority for the adoption of regulations by the board is found in § 54.1-2400 of the Code of Virginia. If there is other legal authority for promulgation of a regulation, please provide that Code reference. § 54.1-3404. Inventories of controlled substances required of certain persons; contents and form of record.

**Signature:**

**Date:** 5/27/11



# COMMONWEALTH OF VIRGINIA Board of Health Professions

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Richmond, Virginia 23233-1463

(804) 367-4603 (Tel)  
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## Petition for Rule-making

*The Code of Virginia (§ 2.2-4007) and the Public Participation Guidelines of this board require a person who wishes to petition the board to develop a new regulation or amend an existing regulation to provide certain information. Within 14 days of receiving a valid petition, the board will notify the petitioner and send a notice to the Register of Regulations identifying the petitioner, the nature of the request and the plan for responding to the petition. Following publication of the petition in the Register, a 21-day comment period will begin to allow written comment on the petition. Within 90 days after the comment period, the board will issue a written decision on the petition.*

**Please provide the information requested below. (Print or Type)**

Petitioner's full name (Last, First, Middle initial, Suffix,)

Annette Basler Reichenbaugh

Street Address  
5360 Ashleigh Rd

Area Code and Telephone Number  
703-689-9036

City  
Fairfax

State  
VA

Zip Code  
22030

Email Address (optional)  
Annette.Reichenbaugh@hcahealthcare.com

Fax (optional)  
703-689-9110

### Respond to the following questions:

1. What regulation are you petitioning the board to amend? Please state the title of the regulation and the section/sections you want the board to consider amending.

18VAC110-20-490. Automated devices for dispensing and administration of drugs.

Section 5

5.a - covers reconciliation of all quantities of Schedule II thru V

5.b - covers each device per month all patients for a time period of not less than 24 consecutive hours.

2. Please summarize the substance of the change you are requesting and state the rationale or purpose for the new or amended rule.

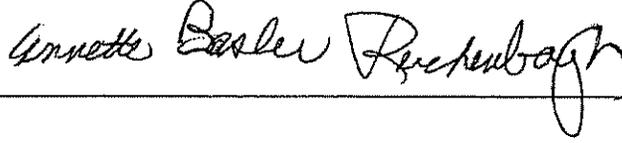
- 1). I recommend reviewing the overrides daily looking for trends
- 2). Utilize Rx Auditor report to determine if a focus review is necessary . . . Based on specific criteria.
- 3). Perform a focused review

3. State the legal authority of the board to take the action requested. In general, the legal authority for the adoption of regulations by the board is found in § 54.1-2400 of the Code of Virginia. If there is other legal authority for promulgation of a regulation, please provide that Code reference.

None

**Signature:**

Annette Basler Reichenbaugh



Date: May 16, 2011

## Townhall Comments on Petitions for Rulemaking

### Automated Dispensing Devices

**Commenter:** Mary Scott Garrett Parham Doctors' Hospital \*

I fully support this change. Technology has become so much more sophisticated that expiration dates are readily retrievable and problems with drawers identified via automatic notification on the cabinet, with error messages on the main console. There is little need for monthly review by the pharmacy staff.

6/20/11  
17655

**Commenter:** Joe Ciezkowski, Director of Pharmacy, LewisGale Medical Center \*

#### Comment on petition to amend requirements for reviewing automated dispensing machines

I support the proposed regulation amendment for the following reasons:

1. Hospital pharmacies have quality control systems in place to look for many of the same items that are required by the Board in 18VAC 110-20-490. However, it is rare that these quality control audits must be done monthly, since variance is unusual. While I agree that these audits are important and necessary, requiring that the audits be performed monthly is time-consuming, and takes away time that could be used for other, more productive, activities.
2. Specifically, 18VAC 110-20-490.5 requires monthly audits for 5 items that are actually reviewed by virtue of the very use of the machines. Outdated drugs, location of drugs within the device, etc., are vital components of the drug delivery system, and must be part of the day-to-day operation of the department. It would be more useful for the Board to know that the drug distribution system addresses these items on an ongoing basis than to see the results of monthly audits.

I hope the Board will consider revising these requirements.

6/21/11  
17658

**Commenter:** Anita Atkins, CJW Medical Center--JW Campus \*

#### Automated Dispensing Cabinets in Hospitals

I fully support the changes proposed for the regulation. Automation offers mechanisms for expiration dates to be monitored, security to remain in tact, and ability to run audit reports as needed.

6/28/11  
17665

**Commenter:** Karen Dunavant, Reston Hospital Center \*

#### Comment on Petition for change to Automated Dispensing Cabinet requirements

I fully support a change in 18VAC110-20-490 section 5. The current process takes 40 to 60 man-hours each month to complete all audits required and does not identify possible diversion effectively.

Using a reconciliation software program similar to RxAuditor, Pandora or others - a 24-hour audit of all transactions for controlled substances becomes obsolete. These programs show statistical analysis over a month. Using the process set by the regulation, identifying possible diversion was hit or miss. Using

RxAuditor, we can identify specific employees to audit based on peer-to-peer comparisons of use for their unit. This is a more effective use of the auditors time and addresses the diversion concerns.

Combine this with a facility using their ADC on "profile" mode, where a pharmacist must enter the order into the hospital's Clinical System before the drug is available to the nurse (order verification). The use of Controlled Substance perpetual inventory management systems (i.e. CII-Safe, NarcStation, etc) where issues remain open until appropriately stocked into the receiving ADC (narrowing the focus of audits for issue/restock). Overrides and Open Discrepancies may be reviewed easily and in a more timely manner.

Thank you for your consideration.

6/28/11  
17666

**Commenter:** Karen Dunavant, Reston Hospital Center \*

**Comment on Petition for change to Automated Dispensing Cabinet requirements**

I fully support a change in 18VAC110-20-490 section 5. The current process takes 40 to 60 man-hours each month to complete all audits required and does not identify possible diversion effectively.

Using a reconciliation software program similar to RxAuditor, Pandora or others - a 24-hour audit of all transactions for controlled substances becomes obsolete. These programs show statistical analysis over a month. Using the process set by the regulation, identifying possible diversion was hit or miss. Using RxAuditor, we can identify specific employees to audit based on peer-to-peer comparisons of use for their unit. This is a more effective use of the auditors time and addresses the diversion concerns.

Combine this with a facility using their ADC on "profile" mode, where a pharmacist must enter the order into the hospital's Clinical System before the drug is available to the nurse (order verification). The use of Controlled Substance perpetual inventory management systems (i.e. CII-Safe, NarcStation, etc) where issues remain open until appropriately stocked into the receiving ADC (narrowing the focus of audits for issue/restock). Overrides and Open Discrepancies may be reviewed easily and in a more timely manner.

Thank you for your consideration.

7/7/11  
17682

**Commenter:** Dana H. Anderson, Virginia Hospital Center \*

**Comment on Petition for change to Automated Dispensing Cabinets**

I fully support a change in 18VAC110-20-490 section 5. My facility has 72 unique ADC locations and requires a full time pharmacy employee to perform the 24 hour audits. These audits are not an effective method of identifying potential diversion as the audit is a 24 hour snap shot within a months worth of activity.

I currently utilize a program that does statistical analysis on controlled substance activity over a 30 day period. This statistical report identifies specific employees for each unique location and compares activity peer-to-peer. This is an efficient and effective process and reviews a broader time frame to identify potential diversion.

In addition, orders are reviewed by a pharmacist and entered into the electronic MAR prior to the end user having access to the medication. The use of a Controlled Substance perpetual inventory management system provides additional safe guards for potential diversion review.

I appreciate your consideration of this petition.

7/7/11  
17683

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**Commenter:** Michael Nyame-Mireku, Virginia Hospital Center \*

**Comment on Petition for change to Automated Dispensing Cabinet requirements**

I am completely in support of changing 18VAC110-20-490 section 5. With increasing use of eMAR, CPOE, and other third party monitoring programs, users could effectively and efficiently be tracked and monitored. C2 Safe now allows perpetual inventory of controlled substances with easy electronic auditing.

The number of Pyxis machines being used in hospitals have increased significantly, requiring significant resources to keep up with the paper auditing.

I appreciate your consideration of this petition.

7/7/11  
17684

**Commenter:** Noel Hodges, HCA Virginia \*

**18VAC110-20-490**

I am in full support to change 18VAC110-20-490 section 5. The current process takes valuable pharmacist man-hours each month that could be used to promote patient care.

The manual audits required are not the most effective or efficient way to identify possible diversion. Using a reconciliation software program (i.e. RxAuditor, Pandora) quickly provides an audit of all transactions for controlled substances. These programs show statistical analysis for each user and medication. Using such a system, pharmacies can identify specific employees to audit based on peer-to-peer comparisons.

Thank you for your consideration.

7/7/11  
17685

**Commenter:** Margaret Rowe Fauquier Health \*

**Proposed change r/t auditing ADD's on a monthly basis**

I would like to add my voice to those who have already commented in favor of this change. I feel that the process of performing these audits consumes valuable resources with very little to show for the effort in terms of uncovering diversion. Systems such as Pandora or RxAuditor provide much more powerful and statistically relevant data for us.

Thank you!

7/7/11  
17686

**Commenter:** Margaret Rowe Fauquier Health \*

**Proposed change r/t auditing ADD's on a monthly basis**

I would like to add my voice to those who have already commented in favor of this change. I feel that the process of performing these audits consumes valuable resources with very little to show for the effort in terms of uncovering diversion. Systems such as Pandora or RxAuditor provide much more powerful and statistically relevant data for us.

Thank you!

7/7/11  
17688

**Commenter:** Deborah Smith, PharmD, Director of Pharmacy, LewisGale Montgomery \*

**Consideration of Automated Dispensing Audit.**

As a longterm Pharmacist who has worked in a variety of settings I have had the opportunity to explore the potential requirements of the monthly audits as currently outlined.

In the face of diverse checks and balances in place provided by automated dispensing cabinets daily as well as services such as RX Auditor, I find the additional auditing currently in the regs duplicative and labor-intense. In addition reports such as Compare within PYXIS as well as daily all station reports for controlled substances, we have capability to already do this process on a prospective basis in our daily functions.

I am happy to expand upon this should additional information be required.

I therefore respectfully request consideration to consider this audit requirement a limitation rather than enhancement of monitoring in the face of current automation as we know it in pharmacy practice

Thank you for your consideration.

7/8/11  
17692

**Commenter:** Frederik Friis

**Comment on Petition for change to Automated Dispensing Cabinet requirements (Like Mr Caren donavan)**

I agree with you Mr Caren donavan, i think I fully support a change in 18VAC110-20-490 section 5. The current process takes 40 to 60 man-hours each month to complete all audits required and does not identify possible diversion effectively.

Using a reconciliation software program similar to RxAuditor, Pandora or others - a 24-hour audit of all transactions for controlled substances becomes obsolete. These programs show statistical analysis over a month. Using the process set by the regulation, identifying possible diversion was hit or miss. Using RxAuditor, we can identify specific employees to audit based on peer-to-peer comparisons of use for their unit. This is a more effective use of the auditors time and addresses the diversion concerns.

Combine this with a facility using their ADC on "profile" mode, where a pharmacist must enter the order into the hospital's Clinical System before the drug is available to the nurse (order verification). The use of Controlled Substance perpetual inventory management systems (i.e. CII-Safe, NarcStation, etc) where issues remain open until appropriately stocked into the receiving ADC (narrowing the focus of audits for issue/restock). Overrides and Open Discrepancies may be reviewed easily and in a more timely manner.

Thank you for your consideration.

Makeityourring Diamond Engagement Rings

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Virginia  
Regulatory  
Town Hall

townhall.virginia.gov

## Notice of Intended Regulatory Action (NOIRA) Agency Background Document

<b>Agency name</b>	Board of Pharmacy, Department of Health Professions
<b>Virginia Administrative Code (VAC) citation</b>	18VAC110-20-10 et seq.
<b>Regulation title</b>	Regulations Governing the Practice of Pharmacy
<b>Action title</b>	Modifications to requirements for automated dispensing devices
<b>Date this document prepared</b>	9/23/11

This information is required for executive branch review and the Virginia Registrar of Regulations, pursuant to the Virginia Administrative Process Act (APA), Executive Orders 14 (2010) and 58 (1999), and the *Virginia Register Form, Style, and Procedure Manual*.

### Purpose

*Please describe the subject matter and intent of the planned regulatory action. Also include a brief explanation of the need for and the goals of the new or amended regulation.*

The Board of Pharmacy received three petitions for rulemaking from hospital pharmacists requesting an amendment to #5 of section 490 in Chapter 20, which provides requirements for automated devices for dispensing and administration of drugs. The petitioners requested less burdensome requirements for verification of storage, location, expiration dates, drug security and validity of access codes.

While the Board agreed that the petition was reasonable and the specific requirements in #5 may need to be modified for consistency with current technology, it concluded that all of section 490 should be examined for possible amendments that would ensure drug security and integrity but would make compliance less burdensome.

### Legal basis

*Please identify the state and/or federal legal authority to promulgate this proposed regulation, including (1) the most relevant law and/or regulation, including Code of Virginia citation and General Assembly chapter number(s), if applicable, and (2) promulgating entity, i.e., agency, board, or person. Describe the legal authority and the extent to which the authority is mandatory or discretionary.*

Regulations are promulgated under the general authority of Chapter 24 of Title 54.1 of the Code of Virginia. Section 54.1-2400, which provides the Board of Pharmacy the authority to promulgate regulations:

**§ 54.1-2400 -General powers and duties of health regulatory boards**

*The general powers and duties of health regulatory boards shall be:*

...  
6. *To promulgate regulations in accordance with the Administrative Process Act (§ 9-6.14:1 et seq.) which are reasonable and necessary to administer effectively the regulatory system. Such regulations shall not conflict with the purposes and intent of this chapter or of Chapter 1 (§ 54.1-100 et seq.) and Chapter 25 (§ 54.1-2500 et seq.) of this title. ...*

The specific statutory authority for the Board of Pharmacy to regulate the practice of pharmacy including regulations pertaining to the safety and integrity of drugs is found in § 54.1-3307 of the Code of Virginia.

**§ 54.1-3307. Specific powers and duties of Board.**

*The Board shall regulate the practice of pharmacy and the manufacturing, dispensing, selling, distributing, processing, compounding, or disposal of drugs and devices. The Board shall also control the character and standard of all drugs, cosmetics and devices within the Commonwealth, investigate all complaints as to the quality and strength of all drugs, cosmetics, and devices and take such action as may be necessary to prevent the manufacturing, dispensing, selling, distributing, processing, compounding and disposal of such drugs, cosmetics and devices which do not conform to the requirements of law. In so regulating the Board shall consider any of the following criteria as they are applicable:*

- 1. Maintenance of the quality, quantity, integrity, safety and efficacy of drugs or devices distributed, dispensed or administered.*
- 2. Compliance with the prescriber's instructions regarding the drug, its quantity, quality and directions for use.*
- 3. Controls and safeguards against diversion of drugs or devices.*
- 4. Maintenance of the integrity of, and public confidence in, the profession and improving the delivery of quality pharmaceutical services to the citizens of Virginia.*
- 5. Maintenance of complete records of the nature, quantity or quality of drugs or substances distributed or dispensed, and of all transactions involving controlled substances or drugs or devices so as to provide adequate information to the patient, the practitioner or the Board.*
- 6. Control of factors contributing to abuse of legitimately obtained drugs, devices, or controlled substances.*
- 7. Promotion of scientific or technical advances in the practice of pharmacy and the manufacture and distribution of controlled drugs, devices or substances.*
- 8. Impact on costs to the public and within the health care industry through the modification of mandatory practices and procedures not essential to meeting the criteria set out in subdivisions 1 through 7 of this section.*

9. Such other factors as may be relevant to, and consistent with, the public health and safety and the cost of rendering pharmacy services.

**Need**

*Please detail the specific reasons why the agency has determined that the proposed regulatory action is essential to protect the health, safety, or welfare of citizens. In addition, delineate any potential issues that may need to be addressed as the regulation is developed.*

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As one of the petitioners stated, automation has been designed and updated to improve drug storage, security and safety, while streamlining work processes and increasing efficiencies. Advancements in technology can accommodate verification requirements that currently require manual processes. The Board will consider changes to the process and/or parameters to decrease the amount of time required to comply with monthly audits. Certain software that analyses automated dispensing machine transactions could substitute for some of the manual reconciliation process. Hospitals report that the software reports can more quickly and efficiently identify possible diversions from the machines. Taking advantage of technology to replace some of the manual processes appears to be advisable for public health and safety because it could allow pharmacists to spend more time focused on patient care and still continue to protect against diversion.

**Substance**

*Please detail any changes that will be proposed. For new regulations, include a summary of the proposed regulatory action. Where provisions of an existing regulation are being amended, explain how the existing regulation will be changed.*

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The petitioners requested modifications to #5 of section 490 to change the requirement that automated dispensing devices must be inspected monthly by pharmacy personnel to verify proper storage, proper location of drugs within the device, expiration dates the security of drugs and validity of access codes. Devices with technology that has certain capabilities would not require the same manual verification in a monthly inspection. However, the pharmacy would conduct a focused review on overrides or transactions that are outside the norm.

In addition to consideration of changes recommended by the petitioners, the Committee will review all of section 490 for less burdensome alternatives or clarifications consistent with current technology and public safety.

**Alternatives**

*Please describe all viable alternatives to the proposed regulatory action that have been or will be considered to meet the essential purpose of the action. Also, please describe the process by which the agency has considered or will consider other alternatives for achieving the need in the most cost-effective manner.*

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To be responsive to the petitions for rulemaking and the need to review the requirements for less burdensome options, there are no alternatives other than regulatory action.

### Public participation

*Please indicate whether the agency is seeking comments on the intended regulatory action, including ideas to assist the agency in the development of the proposal and the costs and benefits of the alternatives stated in this notice or other alternatives. Also, indicate whether a public hearing is to be held to receive comments on this notice.*

The agency/board is seeking comments on the intended regulatory action to replace the emergency regulations with permanent regulations, including but not limited to 1) ideas to assist in the development of a proposal, 2) the costs and benefits of the alternatives stated in this background document or other alternatives and 3) potential impacts of the regulation. The agency/board is also seeking information on impacts on small businesses as defined in § 2.2-4007.1 of the Code of Virginia. Information may include 1) projected reporting, recordkeeping and other administrative costs, 2) probable effect of the regulation on affected small businesses, and 3) description of less intrusive or costly alternative methods of achieving the purpose of the regulation.

Anyone wishing to submit written comments may send them to Elaine Yeatts at the Department of Health Professions, 9960 Mayland Drive, Suite 300, Richmond, VA 23233 or [Elaine.yeatts@dhp.virginia.gov](mailto:Elaine.yeatts@dhp.virginia.gov) or by fax to (804) 527-4434 or by posting on the Regulatory Townhall at [www.townhall.virginia.gov](http://www.townhall.virginia.gov). Written comments must include the name and address of the commenter. In order to be considered comments must be received by the last day of the public comment period on the Notice of Intended Regulatory Action.

At the conclusion of the NOIRA comment, the Board will adopt proposed regulations. A public meeting will be held and notice of the meeting will be found in the Calendar of Events section of the Virginia Register of Regulations after Executive Branch review and approval to open the regulation for 60 days of public comment. Both oral and written comments may be submitted at that time.

### Participatory approach

*Please indicate, to the extent known, if advisers (e.g., ad hoc advisory committees, regulatory advisory panels) will be involved in the development of the proposed regulation. Indicate that 1) the agency is not using the participatory approach in the development of the proposal because the agency has authorized proceeding without using the participatory approach; 2) the agency is using the participatory approach in the development of the proposal; or 3) the agency is inviting comment on whether to use the participatory approach to assist the agency in the development of a proposal.*

The Board will utilize the participatory approach as members of the Regulation Committee will review section 490 on automated dispensing devices, since its membership includes persons with expertise in hospital pharmacy systems. Additionally, pharmacy staff of the Board have expertise in automated devices and will be able to offer advice in the process. The Virginia Society of Hospital Pharmacies will be invited to attend and participate in the development of regulatory language, and public comment will be encouraged as the Committee considers changes to the regulation.

### Family impact

*Assess the potential impact of the proposed regulatory action on the institution of the family and family stability including to what extent the regulatory action will: 1) strengthen or erode the authority and rights of parents in the education, nurturing, and supervision of their children; 2) encourage or discourage economic self-sufficiency, self-pride, and the assumption of responsibility for oneself, one's spouse, and one's children and/or elderly parents; 3) strengthen or erode the marital commitment; and 4) increase or decrease disposable family income.*

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There is no impact of the proposed regulatory action on the institution of the family and family stability.

## RESEARCH – Automated Dispensing Devices

- Surveyed states to determine which states were pleased with their language regarding auditing requirements for automated dispensing devices – OH, TX, MN, and MD
- Committee needs only to identify key concepts it may change in regulation, however, underlined suggested language is provided below. Suggestions primarily based on suggestions in petitions for rulemaking.
- Regulation must comply with statutory provisions of § 54.1-3434.02. Specific auditing requirements highlighted.
- Discuss whether similar changes should be made to Regulation 18VAC110-20-555 regarding automated dispensing devices within nursing homes.

### Committee Options:

- Identify key concepts or suggested language for NOIRA that Board may want to change in Regulation 18VAC110-20-490
- Amend NOIRA, if possible, to include similar suggested changes in Regulation 18VAC110-20-555

### § 54.1-3434.02. Automated drug dispensing systems.

A. Hospitals licensed pursuant to Title 32.1 or Title 37.2 may use automated drug dispensing systems, as defined in § 54.1-3401, upon meeting the following conditions:

1. Drugs are placed in the automated drug dispensing system in a hospital and are under the control of a pharmacy providing services to the hospital;
2. The pharmacist-in-charge of the pharmacy providing services to the hospital has established procedures for assuring the accurate stocking and proper storage of drugs in the automated drug dispensing system and for ensuring accountability for and security of all drugs utilized in the automated drug dispensing system until the time such drugs are removed from the automated drug dispensing system for administration to the patients;
3. Removal of drugs from any automated drug dispensing system for administration to patients can only be made pursuant to a valid prescription or lawful order of a prescriber;
4. Adequate security for automated drug dispensing systems is provided, as evidenced by written policies and procedures, for (i) preventing unauthorized access, (ii) complying with federal and state regulations

on prescribing and dispensing controlled substances, (iii) maintaining patient confidentiality, and (iv) assuring compliance with the requirements of this section;

5. Accountability for drugs dispensed from automated drug dispensing systems is vested in the pharmacist-in-charge of a pharmacy located within the hospital or the pharmacist-in-charge of any outside pharmacy providing pharmacy services to the hospital;

6. Filling and stocking of all drugs in automated drug dispensing systems shall be performed under the direction of the pharmacist-in-charge. The task of filling and stocking of drugs into an automated drug dispensing system shall be performed by a pharmacist or a registered pharmacy technician, who shall be an employee of the provider pharmacy and shall be properly trained in accordance with established standards set forth in a policy and procedure manual maintained by the provider pharmacy. The pharmacist stocking and filling the automated drug dispensing system or the pharmacist-in-charge, if the automated drug dispensing system is stocked and filled by a registered pharmacy technician, shall be responsible for the proper and accurate stocking and filling of the automated drug dispensing system.

B. Drugs placed into and removed from automated drug dispensing systems for administration to patients shall be in the manufacturer's or distributor's sealed original packaging or in unit-dose containers packaged by the pharmacy. Drugs in multi-dose packaging, other than those administered orally, may be placed in such a device if approved by the pharmacist-in-charge in consultation with a standing hospital committee comprised of pharmacy, medical, and nursing staff.

C. The pharmacist-in-charge in a pharmacy located within a hospital or the pharmacist-in-charge of any outside pharmacy providing pharmacy services to a hospital shall be responsible for establishing procedures for (i) periodically inspecting and auditing automated drug dispensing systems to assure the proper storage, security, and accountability for all drugs placed in and removed from automated drug dispensing systems, and (ii) reviewing the operation and maintenance of automated drug dispensing systems. This monitoring shall be reviewed by a pharmacist while on the premises of the hospital and in accordance with the pharmacist-in-charge's procedures and the Board of Pharmacy's regulations.

D. The Board of Pharmacy shall promulgate regulations establishing minimum requirements for random periodic inspections and monthly audits of automated drug dispensing systems to assure the proper storage, security, and accountability of all drugs placed in and removed from automated drug dispensing systems and for reviewing the operation and maintenance of automated drug dispensing systems.

(1999, c. 750; 2004, c. 140; 2009, c. 100.)

#### **18VAC110-20-490. Automated devices for dispensing and administration of drugs.**

A hospital may use automated devices for the dispensing and administration of drugs pursuant to § 54.1-3301 of the Code of Virginia and §§ 54.1-3401 and 54.1-3434.02 of the Drug Control Act and in accordance with 18VAC110-20-270, 18VAC110-20-420, or 18VAC110-20-460 as applicable. The following conditions shall apply:

1. Prior to removal of drugs from the pharmacy, a delivery record shall be generated for all drugs to be placed in an automated dispensing device which shall include the date; drug name, dosage form, and strength; quantity; hospital unit and a unique identifier for the specific device

receiving the drug; initials of the person loading the automated dispensing device; and initials of the pharmacist checking the drugs to be removed from the pharmacy and the delivery record for accuracy.

2. Automated dispensing devices in hospitals shall be capable of producing a hard-copy record of distribution which shall show patient name, drug name and strength, dose withdrawn, dose to be administered, date and time of withdrawal from the device, and identity of person withdrawing the drug.

3. The PIC or his designee shall conduct at least a monthly audit to review distribution and administration of Schedule II through V drugs from each automated dispensing device as follows:

a. The audit shall reconcile records of all quantities of Schedule II through V drugs dispensed from the pharmacy with records of all quantities loaded into each device to detect whether any drugs recorded as removed from the pharmacy were diverted rather than being placed in the proper device.

b. A discrepancy report shall be generated for each discrepancy in the count of a drug on hand in the device. Each such report shall be resolved by the PIC or his designee within 72 hours of the time the discrepancy was discovered or, if determined to be a theft or an unusual loss of drugs, shall be immediately reported to the board in accordance with § 54.1-3404 E of the Drug Control Act.

c. The audit shall include a review of a sample of administration records from each device per month for possible diversion by fraudulent charting. A sample shall include all Schedule II-V drugs administered for a time period of not less than 24 consecutive hours during the audit period.

d. The audit shall include a check of medical records to ensure that a valid order exists for a random sample of doses recorded as administered, unless the device uses a "profile" mode wherein a pharmacist must verify the data entry of the order into the pharmacy's automated data processing system prior to an individual gaining access to the drug in the device.

e. The audit shall also check for compliance with written procedures for security and use of the automated dispensing devices, accuracy of distribution from the device, and proper recordkeeping.

f. The hard-copy distribution and administration records printed out and reviewed in the audit shall be initialed and dated by the person conducting the audit. If nonpharmacist personnel conduct the audit, a pharmacist shall review the record and shall initial and date the record.

g. The PIC or his designee shall be exempt from the audit requirements in 3a and 3c of this subsection if reconciliation software which provides a statistical analysis over a period of time based on peer-to-peer comparisons of use for that unit or department and perpetual inventory management software for monitoring drugs in Schedules II-V which monitors overrides and

open discrepancies is used to identify suspicious activity. A focused audit of the suspicious activity and individuals associated with the activity shall be performed at least monthly.

4. If an automated dispensing device is used to obtain drugs for dispensing from an emergency room, a separate dispensing record is not required provided the automated record distinguishes dispensing from administration and records the identity of the physician who is dispensing.

5. Automated dispensing devices shall be inspected monthly by pharmacy personnel to verify proper storage, proper location of drugs within the device, expiration dates, the security of drugs and validity of access codes. Such monthly inspection shall not require physical inspection of the device if the device is capable of and performs the following:

- a. continuous monitoring of proper storage with documented temperature ranges, variances, and resolutions;
- b. automatically identifies and isolates the location of each drug within the device using barcode technology and generates a report verifying the applicable settings;
- c. automatically tracks drug expiration dates and generates proactive reports allowing for the replacement of drugs prior to their expiration date;
- d. electronically detects the opening of the device, identifies the person accessing the device, automatically denies access to the device during malfunctions and mechanical errors, and generates reports of any malfunction and mechanical error; and,
- e. verifies access codes using biometric identification or other coded identification after the initial log-on in order to eliminate sharing or theft of access codes.

6. Personnel allowed access to an automated dispensing device shall have a specific access code which records the identity of the person accessing the device.

7. Proper use of the automated dispensing devices and means of compliance with requirements shall be set forth in the pharmacy's policy and procedure manual.

8. All records required by this section shall be filed in chronological order from date of issue and maintained for a period of not less than two years. Records shall be maintained at the address of the pharmacy providing services to the hospital except:

a. Manual Schedule VI distribution records may be maintained in offsite storage or electronically as an electronic image that provides an exact image of the document that is clearly legible provided such offsite or electronic records are retrievable and made available for inspection or audit within 48 hours of a request by the board or an authorized agent.

b. Distribution and delivery records and required ~~signatures~~ initials may be generated or maintained electronically provided:

(1) The system being used has the capability of recording an electronic signature that is a unique identifier and restricted to the individual required to initial or sign the record.

(2) The records are maintained in a read-only format that cannot be altered after the information is recorded.

(3) The system used is capable of producing a hard-copy printout of the records upon request.

c. Schedule II-V distribution and delivery records may only be stored offsite or electronically as described in subdivisions 9 a and b of this section if authorized by DEA or in federal law or regulation.

d. Hard-copy distribution and administration records that are printed and reviewed in conducting required audits may be maintained at an off-site location or electronically provided they can be readily retrieved upon request; provided they are maintained in a read-only format that does not allow alteration of the records; and provided a separate log is maintained for a period of two years showing dates of audit and review, the identity of the automated dispensing device being audited, the time period covered by the audit and review, and the initials of all reviewers.

#### **18VAC110-20-555. Use of automated dispensing devices.**

**Nursing homes** licensed pursuant to Chapter 5 (§ 32.1-123 et seq.) of Title 32.1 of the Code of Virginia may use automated drug dispensing systems, as defined in § 54.1-3401 of the Code of Virginia, upon meeting the following conditions:

1. Drugs placed in an automated drug dispensing system in a nursing home shall be under the control of the pharmacy providing services to the nursing home, the pharmacy shall have on-line communication with and control of the automated drug dispensing system, and access to any drug for a patient shall be controlled by the pharmacy.

2. A nursing home without an in-house pharmacy shall obtain a controlled substances registration prior to using an automated dispensing system.

3. Removal of drugs from any automated drug dispensing system for administration to patients can only be made pursuant to a valid prescription or lawful order of a prescriber under the following conditions:

a. A drug may not be administered to a patient from an automated dispensing device until a pharmacist has reviewed the prescription order and electronically authorized the access of that drug for that particular patient in accordance with the order.

b. The PIC of the provider pharmacy shall ensure that a pharmacist who has on-line access to the system is available at all times to review a prescription order as needed and authorize administering pursuant to the order reviewed.

c. Drugs that would be stocked in an emergency drug kit pursuant to 18VAC110-20-540 may be accessed prior to receiving electronic authorization from the pharmacist provided that the absence of the drugs would threaten the survival of the patients.

d. Automated dispensing devices shall be capable of producing a hard-copy record of distribution that shall show patient name, drug name and strength, dose withdrawn, dose to be administered, date and time of withdrawal from the device, and identity of person withdrawing the drug.

4. Drugs placed in automated dispensing devices shall be in the manufacturer's sealed original unit dose or unit-of-use packaging or in repackaged unit-dose containers in compliance with the requirements of 18VAC110-20-355 relating to repackaging, labeling, and records.

5. Prior to removal of drugs from the pharmacy, a delivery record shall be generated for all drugs to be placed in an automated dispensing device which shall include the date; drug name, dosage form, and strength; quantity; nursing home; and a unique identifier for the specific device receiving drugs; and initials of pharmacist checking the order of drugs to be removed from the pharmacy and the records of distribution for accuracy.

6. At the direction of the PIC, drugs may be loaded in the device by a pharmacist or a pharmacy technician adequately trained in the proper loading of the system.

7. At the time of loading, the delivery record for all Schedule II through VI drugs shall be signed by a nurse or other person authorized to administer drugs from that specific device, and the record returned to the pharmacy.

8. At the time of loading any Schedule II through V drug, the person loading will verify that the count of that drug in the automated dispensing device is correct. Any discrepancy noted shall be recorded on the delivery record and immediately reported to the PIC, who shall be responsible for reconciliation of the discrepancy or properly reporting of a loss.

9. The PIC or his designee shall conduct at least a monthly audit to review distribution and administration of Schedule II through V drugs from each automated dispensing device as follows:

a. The audit shall reconcile records of all quantities of Schedule II through V drugs dispensed from the pharmacy with records of all quantities loaded into each device to detect whether any drugs recorded as removed from the pharmacy were diverted rather than being placed in the proper device.

b. A discrepancy report shall be generated for each discrepancy in the count of a drug on hand in the device. Each such report shall be resolved by the PIC or his designee within 72 hours of the time the discrepancy was discovered or, if determined to be a theft or an unusual loss of drugs, shall be immediately reported to the board in accordance with § 54.1-3404 E of the Drug Control Act.

c. The audit shall include a review of a sample of administration records from each device per month for possible diversion by fraudulent charting. A sample shall include all Schedule II through V drugs administered for a time period of not less than 24 consecutive hours during the audit period.

d. The audit shall include a check of medical records to ensure that a valid order exists for a random sample of doses recorded as administered.

e. The audit shall also check for compliance with written procedures for security and use of the automated dispensing devices, accuracy of distribution from the device, and proper recordkeeping.

f. The hard-copy distribution and administration records printed out and reviewed in the audit shall be initialed and dated by the person conducting the audit. If nonpharmacist personnel conduct the audit, a pharmacist shall review the record and shall initial and date the record.

10. Automated dispensing devices shall be inspected monthly by pharmacy personnel to verify proper storage, proper location of drugs within the device, expiration dates, the security of drugs and validity of access codes.

11. Personnel allowed access to an automated dispensing device shall have a specific access code which records the identity of the person accessing the device.

12. The PIC of the pharmacy providing services to the nursing home shall establish, maintain, and assure compliance with written policy and procedure for the accurate stocking and proper storage of drugs in the automated drug dispensing system, accountability for and security of all drugs maintained in the automated drug dispensing system, preventing unauthorized access to the system, tracking access to the system, complying with federal and state regulations related to the storage and dispensing of controlled substances, maintaining patient confidentiality, maintaining required records, and assuring compliance with the requirements of this chapter. The manual shall be capable of being accessed at both the pharmacy and the nursing home.

13. All records required by this section shall be filed in chronological order from date of issue and maintained for a period of not less than two years. Records shall be maintained at the address of the pharmacy providing services to the nursing home except:

a. Manual Schedule VI distribution records may be maintained in offsite storage or electronically as an electronic image that provides an exact image of the document that is clearly legible provided such offsite or electronic storage is retrievable and made available for inspection or audit within 48 hours of a request by the board or an authorized agent.

b. Distribution and delivery records and required signatures may be generated or maintained electronically provided:

(1) The system being used has the capability of recording an electronic signature that is a unique identifier and restricted to the individual required to initial or sign the record.

(2) The records are maintained in a read-only format that cannot be altered after the information is recorded.

(3) The system used is capable of producing a hard-copy printout of the records upon request.

c. Schedule II-V distribution and delivery records may only be stored offsite or electronically as described in subdivisions 13 a and b of this section if authorized by DEA or in federal law or regulation.

d. Hard-copy distribution and administration records that are printed and reviewed in conducting required audits may be maintained off site or electronically provided they can be readily retrieved upon request; provided they are maintained in a read-only format that does not allow alteration of the records; and provided a separate log is maintained for a period of two years showing dates of audit and review, the identity of the automated dispensing device being audited, the time period covered by the audit and review, and the initials of all reviewers.

**.10 Quality Assurance Program.**

The permit holder shall maintain a quality assurance program regarding the automated medication system that shall include:

- A. Review of system overrides;
- B. Investigation of medication errors related to the automated medication system;
- C. Review of discrepancies and transaction reports to identify patterns of inappropriate use and access; and
- D. Review of the functioning of the system.

**11 Record Keeping.**

- A. The permit holder and the licensed pharmacist responsible for the automated medication system shall maintain records regarding the system in a readily retrievable manner for at least 2 years.
- B. The records referred to in §A of this regulation shall include:
  - (1) Maintenance records and service logs;
  - (2) System failure reports;
  - (3) Accuracy audits and system performance audits;
  - (4) Copies of reports and analyses generated as part of the quality assurance program;
  - (5) Reports or databases related to level of access and changes in the level of access to the system; and
  - (6) Training records including:
    - (a) Contents of the training program;
    - (b) Dates of training completion; and
    - (c) The identity of those attending the training program.
- C. The permit holder and the licensed pharmacist responsible for the automated medication system shall maintain transaction records for all prescription drugs or devices dispensed or distributed for the preceding 5 years.

# Texas Administrative Code

<u>TITLE 22</u>	EXAMINING BOARDS
<u>PART 15</u>	TEXAS STATE BOARD OF PHARMACY
<u>CHAPTER 291</u>	PHARMACIES
<u>SUBCHAPTER D</u>	INSTITUTIONAL PHARMACY (CLASS C)

## RULE §291.72

## Definitions

The following words and terms, when used in this subchapter, shall have the following meanings, unless the context clearly indicates otherwise.

(5) Automated medication supply system--A mechanical system that performs operations or activities relative to the storage and distribution of medications for administration and which collects, controls, and maintains all transaction information.

## RULE §291.74

## Operational Standards

(2) Automated medication supply systems.

(A) Authority to use automated medication supply systems. A pharmacy may use an automated medication supply system to fill medication orders provided that:

- (i) the pharmacist-in-charge is responsible for the supervision of the operation of the system;
- (ii) the automated medication supply system has been tested by the pharmacy and found to dispense accurately. The pharmacy shall make the results of such testing available to the Board upon request; and
- (iii) the pharmacy will make the automated medication supply system available for inspection by the board for the purpose of validating the accuracy of the system.

(B) Quality assurance program. A pharmacy which uses an automated medication supply system to fill medication orders shall operate according to a written program for quality assurance of the automated medication supply system which:

- (i) requires continuous monitoring of the automated medication supply system; and
- (ii) establishes mechanisms and procedures to test the accuracy of the automated medication supply system at least every six months and whenever any upgrade or change is made to the system and documents each such activity.

(C) Policies and procedures of operation.

 (i) When an automated medication supply system is used to store or distribute medications for administration pursuant to medication orders, it shall be operated according to written policies and procedures of operation. The policies and procedures of operation shall establish requirements for operation of the automated medication supply system and shall describe policies and procedures that:

- (I) include a description of the policies and procedures of operation;
- (II) provide for a pharmacist's review and approval of each original or new medication order prior to withdrawal from the automated medication supply system:

(-a-) before the order is filled when a pharmacist is on duty except for an emergency order;  
(-b-) retrospectively within 72 hours in a facility with a full-time pharmacist when a pharmacist is not on duty at the time the order is made; or

(-c-) retrospectively within 7 days in a facility with a part-time or consultant pharmacist when a pharmacist is not on duty at the time the order is made;

(III) provide for access to the automated medication supply system for stocking and retrieval of medications which is limited to licensed healthcare professionals, pharmacy technicians, or pharmacy technician trainees acting under the supervision of a pharmacist;

(IV) provide that a pharmacist is responsible for the accuracy of the restocking of the system. The actual restocking may be performed by a pharmacy technician or pharmacy technician trainee;

(V) provide for an accountability record to be maintained which documents all transactions relative to stocking and removing medications from the automated medication supply system;

(VI) require a prospective or retrospective drug regimen review is conducted as specified in subsection (g) of this section; and

(VII) establish and make provisions for documentation of a preventative maintenance program for the automated medication supply system.

(ii) A pharmacy which uses an automated medication supply system to fill medication orders shall, at least annually, review its written policies and procedures, revise them if necessary, and document the review.

(D) Automated medication supply systems used for storage and recordkeeping of medications located outside of the pharmacy department (e.g., Pyxis). A pharmacy technician or pharmacy technician trainee may re-stock an automated medication supply system located outside of the pharmacy department with prescription drugs provided:

(i) prior to distribution of the prescription drugs a pharmacist verifies that the prescription drugs pulled to stock the automated supply system match the list of prescription drugs generated by the automated medication supply system except as specified in §291.73(e)(2)(C)(ii) of this title; or

(ii) all of the following occur:

(I) the prescription drugs to re-stock the system are labeled and verified with a machine readable product identifier, such as a barcode;

(II) any previous manipulation of the product such as repackaging or extemporaneous compounding has been checked by a pharmacist; and

(III) quality assurance audits are conducted according to established policies and procedures to ensure accuracy of the process.

(E) Recovery Plan. A pharmacy which uses an automated medication supply system to store or distribute medications for administration pursuant to medication orders shall maintain a written plan for recovery from a disaster or any other situation which interrupts the ability of the automated medication supply system to provide services necessary for the operation of the pharmacy. The written plan for recovery shall include:

(i) planning and preparation for maintaining pharmacy services when an automated medication supply system is experiencing downtime;

(ii) procedures for response when an automated medication supply system is experiencing downtime;

(iii) procedures for the maintenance and testing of the written plan for recovery; and

(iv) procedures for notification of the Board and other appropriate agencies whenever an automated medication supply system experiences downtime for more than two days of operation or a period of time which significantly limits the pharmacy's ability to provide pharmacy services.

(3) Verification of medication orders prepared by the pharmacy department through the use of an automated medication supply system. A pharmacist must check drugs prepared pursuant to medication orders to ensure that the drug is prepared for distribution accurately as prescribed. This paragraph does not apply to automated medication supply systems used for storage and recordkeeping of medications located outside of the pharmacy department.

(A) This check shall be considered accomplished if:

(i) a check of the final product is conducted by a pharmacist after the automated system has completed preparation of the medication order and prior to delivery to the patient; or

(ii) the following checks are conducted by a pharmacist:

(I) if the automated medication supply system contains unlabeled stock drugs, a pharmacist verifies that those drugs have been accurately stocked; and

(II) a pharmacist checks the accuracy of the data entry of each original or new medication order entered into the automated medication supply system before the order is filled.

(B) If the final check is accomplished as specified in subparagraph (A)(ii) of this paragraph, the following additional requirements must be met.

(i) The medication order preparation process must be fully automated from the time the pharmacist releases the medication order to the automated system until a completed medication order, ready for delivery to the patient, is produced.

(ii) The pharmacy has conducted initial testing and has a continuous quality assurance program which documents that the automated medication supply system dispenses accurately as specified in paragraph (2)(A) and (B) of this subsection.

(iii) The automated medication supply system documents and maintains:

(I) the name(s), initials, or identification code(s) of each pharmacist responsible for the checks outlined in subparagraph (A)(ii) of this paragraph; and

(II) the name(s), initials, or identification code(s) and specific activity(ies) of each pharmacist or pharmacy technician or pharmacy technician trainee who performs any other portion of the medication order preparation process.

(iv) The pharmacy establishes mechanisms and procedures to test the accuracy of the automated medication supply system at least every month rather than every six months as specified in paragraph (2)(B) of this subsection.

[http://info.sos.state.tx.us/pls/pub/readtac\\$ext.TacPage?sl=R&app=9&p\\_dir=&p\\_rloc=&p\\_tloc=&p\\_ploc=&pg=1&p\\_tac=&ti=22&pt=15&ch=291&rl=72](http://info.sos.state.tx.us/pls/pub/readtac$ext.TacPage?sl=R&app=9&p_dir=&p_rloc=&p_tloc=&p_ploc=&pg=1&p_tac=&ti=22&pt=15&ch=291&rl=72)

[http://info.sos.state.tx.us/pls/pub/readtac\\$ext.TacPage?sl=R&app=9&p\\_dir=&p\\_rloc=&p\\_tloc=&p\\_ploc=&pg=1&p\\_tac=&ti=22&pt=15&ch=291&rl=74](http://info.sos.state.tx.us/pls/pub/readtac$ext.TacPage?sl=R&app=9&p_dir=&p_rloc=&p_tloc=&p_ploc=&pg=1&p_tac=&ti=22&pt=15&ch=291&rl=74)

[http://info.sos.state.tx.us/pls/pub/readtac\\$ext.TacPage?sl=T&app=9&p\\_dir=F&p\\_rloc=152138&p\\_tloc=44830&p\\_ploc=29905&pg=4&p\\_tac=&ti=22&pt=15&ch=291&rl=74](http://info.sos.state.tx.us/pls/pub/readtac$ext.TacPage?sl=T&app=9&p_dir=F&p_rloc=152138&p_tloc=44830&p_ploc=29905&pg=4&p_tac=&ti=22&pt=15&ch=291&rl=74)

## “Low Volume” Definition

## RESEARCH – “Low Volume” Definition

- Staff spoke with:
  - Rick Schnatz, Pharm. D., Scientific Liaison (see email)
  - Jim Wagner, Controlled Environment Consulting, former member of 2005-2010 USP Expert Panel with background in testing of any HEPA-filtered device and member of the Board of Directors for Controlled Environment Testing Association (CETA) (see email)
  - Lloyd Allen, USP member

Staff recently realized that “low volume” cannot be defined within a guidance document, because it goes beyond the requirements in Regulation 18VAC110-20-321 which simply adopts USP-NF compounding standards by reference. To define the term, the Board would need to amend the regulation to include a definition and then require compliance with such definition.

### Possible Discussion Points/Questions:

- Point - USP 797 states “When closed-system vial-transfer devices (CSTDs) (i.e., vial-transfer systems that allow no venting or exposure of hazardous substance to the environment) are used, they shall be used within the ISO Class 5 environment of a BSC (biological safety cabinet) or CACI (compounding aseptic containment isolator). The use of a CSTD is preferred because of their inherent closed system process. In facilities that prepare a low volume of hazardous drugs, the use of two tiers of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room) is acceptable.”
- Question – Is the risk to personnel and drug contamination more dependent on the volume of sterile compounding of hazardous drugs being performed or the general sterile compounding practices used by the pharmacy, e.g., prevention of surface contamination?
  - One expert suggests that good general compounding and drug handling practices can significantly prevent harm and contamination.
- Question - If volume of sterile compounding of hazardous drugs in a non-negative pressure room increases exposure and therefore, potential to harm, then what number of compounds may be safely prepared?
  - Prior to final revision of 797, USP considered defining “low volume” as no more than 5 compounds per week or basically 1 compound per day. Per USP expert, the intent of the exemption was for facilities that prepare the occasional hazardous drug (HD) CSP such as methotrexate for ectopic pregnancy or mitomycin eye drops. It was removed in the final version since USP had no scientific justification for the number. If the pharmacy prepares HD CSPs for an active oncology practice, this exemption should not be applied and was not the intent of the committee for a pharmacy to utilize this exemption.

- Because USP is forming an Expert Panel to provide expertise to the current Compounding Expert Committee for writing a new chapter on “Compounding with Hazardous Drugs”, does the Committee wish to recommend to the full Board to wait for USP to potentially define “low volume”?
- If Board attempts to define low volume in regulation, will the number be legally defensible if not based on scientific evidence?
- If Board attempts to define “low volume”, will it potentially be inconsistent with a possible definition from USP in the future?
- Is the Board likely to be successful in defining “low volume” with a specific number in regulation or will possible opposition to requiring pharmacies to build separate rooms for compounding hazardous drugs likely to derail the Board’s efforts?
- Is it appropriate to require in regulation that the burden of proof for establishing a low-volume benchmark be placed on the manufacturer of the engineering control based on independently produced data and studies?
  - This burden of proof was suggested by Mr. Rahe.
  - The validity of his studies is questioned by some.
  - Could the Board sufficiently evaluate various manufacturers’ studies to conclude if valid and appropriate.
- Is there incentive for consultants to facilities building cleanrooms to suggest that the Board define “low volume” since this would strengthen the consultant’s argument that a client should and must create a separate room for sterile compounding of hazardous drugs?

**Possible Options for Committee:**

- Recommend to full board to remove definition for “low volume from guidance document 110-9 as advised by Board counsel and take no further action, understanding that USP may define “low volume” in future.
- Recommend to full board to remove definition for “low volume from guidance document 110-9 as advised by Board counsel and amend Regulation 18VAC110-20-321 to define “low volume” and require compliance with definition.

**18VAC110-20-321. Compounding.**

The compounding of both sterile and non-sterile drug products shall be performed in accordance with USP-NF compounding standards and §54.1-3410.2 of the Code of Virginia.

**§ 54.1-3410.2. Compounding; pharmacists' authority to compound under certain conditions; labeling and record maintenance requirements.**

A. A pharmacist may engage in compounding of drug products when the dispensing of such compounded products is (i) pursuant to valid prescriptions for specific patients and (ii) consistent with the provisions of § 54.1-3303 relating to the issuance of prescriptions and the dispensing of drugs.

Pharmacists shall label all compounded drug products that are dispensed pursuant to a prescription in accordance with this chapter and the Board's regulations, and shall include on the labeling an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding.

B. A pharmacist may also engage in compounding of drug products in anticipation of receipt of prescriptions based on a routine, regularly observed prescribing pattern.

Pharmacists shall label all products compounded prior to dispensing with (i) the name and strength of the compounded medication or a list of the active ingredients and strengths; (ii) the pharmacy's assigned control number that corresponds with the compounding record; (iii) an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding; and (iv) the quantity.

C. In accordance with the conditions set forth in subsections A and B, pharmacists shall not distribute compounded drug products for subsequent distribution or sale to other persons or to commercial entities, including distribution to pharmacies or other entities under common ownership or control with the facility in which such compounding takes place.

A pharmacist may, however, deliver compounded products dispensed pursuant to valid prescriptions to alternate delivery locations pursuant to § 54.1-3420.2.

A pharmacist may also provide compounded products to practitioners of medicine, osteopathy, podiatry, dentistry, or veterinary medicine to administer to their patients in the course of their professional practice, either personally or under their direct and immediate supervision.

Pharmacists shall label all compounded products distributed to practitioners for administration to their patients with (i) the statement "For Administering in Prescriber Practice Location Only"; (ii) the name and strength of the compounded medication or list of the active ingredients and strengths; (iii) the facility's control number; (iv) an appropriate beyond-use date as determined by

the pharmacist in compliance with USP-NF standards for pharmacy compounding; and (v) quantity.

D. Pharmacists shall personally perform or personally supervise the compounding process, which shall include a final check for accuracy and conformity to the formula of the product being prepared, correct ingredients and calculations, accurate and precise measurements, appropriate conditions and procedures, and appearance of the final product.

E. Pharmacists shall ensure compliance with USP-NF standards for both sterile and non-sterile compounding.

F. Pharmacists may use bulk drug substances in compounding when such bulk drug substances:

1. Comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if such monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding; or are drug substances that are components of drugs approved by the FDA for use in the United States; or are otherwise approved by the FDA;
2. Are manufactured by an establishment that is registered by the FDA; or
3. Are distributed by a licensed wholesale distributor or registered nonresident wholesale distributor, or are distributed by a supplier otherwise approved by the FDA to distribute bulk drug substances if the pharmacist can establish purity and safety by reasonable means, such as lot analysis, manufacturer reputation, or reliability of the source.

G. Pharmacists may compound using ingredients that are not considered drug products in accordance with the USP-NF standards and guidance on pharmacy compounding.

H. Pharmacists shall not engage in the following:

1. The compounding for human use of a drug product that has been withdrawn or removed from the market by the FDA because such drug product or a component of such drug product has been found to be unsafe. However, this prohibition shall be limited to the scope of the FDA withdrawal; or
2. The regular compounding or the compounding of inordinate amounts of any drug products that are essentially copies of commercially available drug products. However, this prohibition shall not include (i) the compounding of any commercially available product when there is a change in the product ordered by the prescriber for an individual patient, (ii) the compounding of a commercially manufactured drug only during times when the product is not available from the manufacturer or supplier, or (iii) the mixing of two or more commercially available products regardless of whether the end product is a commercially available product.

I. Pharmacists shall maintain records of all compounded drug products as part of the prescription, formula record, formula book, or other log or record. Records may be maintained electronically, manually, in a combination of both, or by any other readily retrievable method.

1. In addition to other requirements for prescription records, records for products compounded pursuant to a prescription order for a single patient where only manufacturers' finished products

are used as components shall include the name and quantity of all components, the date of compounding and dispensing, the prescription number or other identifier of the prescription order, the total quantity of finished product, the signature or initials of the pharmacist or pharmacy technician performing the compounding, and the signature or initials of the pharmacist responsible for supervising the pharmacy technician and verifying the accuracy and integrity of compounded products.

2. In addition to the requirements of subdivision I 1, records for products compounded in bulk or batch in advance of dispensing or when bulk drug substances are used shall include: the generic name and the name of the manufacturer of each component or the brand name of each component; the manufacturer's lot number and expiration date for each component or when the original manufacturer's lot number and expiration date are unknown, the source of acquisition of the component; the assigned lot number if subdivided, the unit or package size and the number of units or packages prepared; and the beyond-use date. The criteria for establishing the beyond-use date shall be available for inspection by the Board.

3. A complete compounding formula listing all procedures, necessary equipment, necessary environmental considerations, and other factors in detail shall be maintained where such instructions are necessary to replicate a compounded product or where the compounding is difficult or complex and must be done by a certain process in order to ensure the integrity of the finished product.

4. A formal written quality assurance plan shall be maintained that describes specific monitoring and evaluation of compounding activities in accordance with USP-NF standards. Records shall be maintained showing compliance with monitoring and evaluation requirements of the plan to include training and initial and periodic competence assessment of personnel involved in compounding, monitoring of environmental controls and equipment calibration, and any end-product testing, if applicable.

J. Practitioners who may lawfully compound drugs for administering or dispensing to their own patients pursuant to §§ 54.1-3301, 54.1-3304 and 54.1-3304.1 shall comply with all provisions of this section and the relevant Board regulations.

(2003, c. 509; 2005, c. 200.)

Major Deficiency	Law/Reg Cite	Conditions	\$ Penalty
18. Records of dispensing not maintained as required	54.1-3404, 18VAC110-20-240, 18VAC110-20-250, 18VAC110-20-420, and 18VAC110-20-425		250
19. Pharmacists not verifying or failing to document verification of accuracy of dispensed prescriptions	18VAC110-20-270, 18VAC110-20-420 and 18VAC110-20-425	10% threshold for documentation	500
20. Pharmacist not checking and documenting repackaging, compounding, or bulk packaging	54.1-3410.2, 18VAC110-20-355 and 18VAC110-20-425	10% threshold	250
21. No clean room	54.1-3410.2		5000
22. Certification of the direct compounding area (DCA) for CSPs indicating ISO Class 5 over 60 days late (6mo + 60 days)	54.1-3410.2		3000
23. Certification of the buffer or clean room and ante room indicating ISO Class 7 / ISO Class 8 or better over 60 days late (6mo+60 days). Corrective action not taken within one month of certification report.	54.1-3410.2	Review 2 most recent reports	1000
24. Sterile compounding of hazardous drugs performed in an area not physically separated from other preparation areas.	54.1-3410.2	Low volume defined as 15 or less hazardous drug CSP/week or as defined by USP. Review 2 months records.	2000
25. No documentation of sterilization methods or endotoxin pyrogen testing for high-risk level CSPs; or, no documentation of initial and semi-annual media-fill testing for persons performing high-risk level CSPs; or, documentation that a person who failed a media-fill test has performed high-risk level CSPs after receipt of the negative test result and prior to retraining and receipt of passing media-fill test; or, high-risk drugs intended for use are improperly stored.	54.1-3410.2		5000 per incident within previous 30 days



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Juran, Caroline (DHP)

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**Subject:** FW: "low volume" - Need Assistance

From: Rick Schnatz [mailto:RXS@usp.org]  
Sent: Friday, November 11, 2011 10:59 AM  
To: Juran, Caroline (DHP)  
Subject: Re: "low volume" - Need Assistance

Hi Caroline,

It is nice to hear from you. Hopefully I'll be able to assist in answering some of your questions.

Please see comments below.

CETA, the Controlled Environment Testing Association, is devoted to promoting and developing quality assurance within the controlled environment testing industry.

>>> "Juran, Caroline (DHP)" <Caroline.Juran@DHP.VIRGINIA.GOV> 11/11/2011 2:06 AM >>>  
Rick,

We met this past Spring at the NABP Annual meeting and I'm hoping you can assist me.

Below is an excerpt taken from the last full board meeting of the Virginia Board of Pharmacy. As you can see, the Board has requested that I contact industry experts to gather more information for consideration of a "low volume" definition and the claims made by Containment Technologies Group, Inc. that a Containment Aseptic Compounding Isolator (CACI) can be used to compound a much larger volume of hazardous drugs than a Class II biological safety cabinet.

Could you please provide me with the minutes or specific information from the USP experts discussions which led to the conclusion to eliminate a definition of low volume in the final revision?

The Sterile Compounding Expert Committee in the last cycle (2005-2010) concluded that there was no scientific evidence to support "a number" to define low volume. The current Compounding Expert Committee is in the process of writing a new chapter on "Compounding with Hazardous Drugs". In that effort they are forming an Expert Panel (EP) to help provide expertise in this area. One of the questions for this EP will be if there is data to support inserting a number in the revision to Chapter <797>. As in USP policy all revisions will be posted on our web site in Pharmacopial Forum for public comment.

Eric Kastango indicated to us this past summer that USP did not define low volume since there was no scientific data to support a particular number. Is this still the case or is USP planning to review this issue again?

As above, Eric's statement is correct. Also, as above, USP is planning to revisit and review this issue again.

Besides USP, who are some other "industry experts" that could offer comment for the Board for consideration, i.e., is there a professional association for engineering control technology, or does NIOSH have any standards for how many HD CSPs may be safely compounded?

ASHP might be a source of information on HDs. Their document is titled: ASHP Guidelines on Handling Hazardous Drugs. I've attached a copy for your reference. Also, Mr. Jim Wagner, a former member of our Sterile Compounding Expert Committee, is quite knowledgeable in this area. His contact information is: James T Wagner  
jimwagner@cenvironment.com Telephone: 484-852-0310

CETA is the Controlled Environment Testing Association. They are devoted to promoting and developing quality assurance within the controlled environment testing industry. They may be a source to investigate as well.

I hope this information will be of help. Please call if I can be of further service.

Regards,

Rick

Any information would be a great help. Unfortunately, I'm under a deadline, therefore, a response by November 14th or 15th would be greatly appreciated.

- Request for Consideration of Amending Guidance Document 110-9, Major 24 regarding Definition of "Low Volume": Ms. Juran reminded the Board that USP Chapter 797 allows sterile compounding of hazardous drugs in an area not physically separated from other preparation areas if the compounding of hazardous drugs is limited to a "low volume". To offer guidance to the inspectors, the Board had defined "low volume" at the June board meeting to mean no more than 15 compounded hazardous preparations per week or as defined by USP. Subsequent to the June board meeting the Board received a letter from Hank Rahe, Technical Director, Containment Technologies Group, Inc., requesting the Board amend the definition of "low volume" in Guidance Document 110-9, Major 24, to place the burden of proof on the manufacturer of the engineering control to state the low-volume benchmark based on independently produced data and studies. Mr. Rahe was present at the board meeting and offered comment that with the use of a Containment Aseptic Compounding Isolator (CACI) a much larger volume of hazardous drugs can be compounded safely compared to a Class II biological safety cabinet. Motion: The Board voted unanimously to refer the request for amending the definition of "low volume" in Guidance Document 110-9, Major 24, to the regulation committee for further review and for Board staff to obtain any additional information from industry experts for consideration by the committee and full Board. (motion by Shinaberry, second by Allen)

Thank you.

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Juran, Caroline (DHP)

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**From:** Jim Wagner [jimwagner@cenvironment.com]  
**Sent:** Friday, November 18, 2011 10:33 AM  
**To:** Juran, Caroline (DHP)  
**Subject:** FW: "low volume" - Need Assistance  
**Attachments:** Vial Surface contamination.pdf; Cytotoxic Drug Residues Sti .pdf; 622 ASHP unidirectional air flow 2007.pdf; CAG-008-2010\_1.pdf

Ms. Juran,

I enjoyed our conversation. It brought up a number of issues that were at the core of my professional life for quite a few years. It seems like some disputes never go away. Unfortunately, the challenge you outlined is exactly why I feel guidance with respect to the number of weekly preparations that can qualify for the low-volume exemption is needed. The low-volume exemption is intended for only facilities that do not prepare hazardous drugs as a standard part of their practice. Hazardous drugs are mostly associated with chronic exposure risks. Those who handle hazardous drugs daily or regularly should not be considered low volume. Another issue to remember when discussing this is that the USP low volume exemption includes the use of a closed system transfer device (CSTD). Much of the dialogue I have heard regarding use of this exemption seems to forget that important and costly component.

Isolator manufacturers have a significant financial incentive to make the claim you described below – “my isolator can qualify for the low volume exemption with x number of preparations”. When USP (we – I was part of the sterile compounding committee responsible for the changes) removed the “less than 5 preparations per week” recommendation from the chapter it left the door open for this type of irresponsible marketing. Usually that marketing conveniently forgets to remind the end user that a CSTD is needed.

The primary engineering control (isolator or BSC) is only part of the story when it comes to requiring separate rooms for compounding sterile hazardous drugs. It is assumed all acceptable engineering controls will be able to contain and provide a sterile work environment. The primary engineering control has to meet minimum performance criteria as outlined in CETA CAG-003-2006 per USP Chapter <797> regardless if it is for low or high volume applications. There is no intrinsic difference between the two volume levels when it comes to safe handling. Nor is there anything one manufacturer can do that another can't that would make their isolator uniquely qualified for low-volume applications. Other factors affect the impact on personnel from compounding higher volumes of hazardous drugs. These include: where the drugs are stored, how potential contamination from the outside of hazardous drug vials is handled and what impact that has on the non-hazardous preparations, at what point the primary engineering control must be vented outside the building, etc.

#### **Drug storage:**

The chapter states that hazardous drugs shall be stored separate from other inventory in a manner that prevents contamination in the event of a spill. Hazardous drugs should be stored in a negative pressure room with at least 12 air changes per hour. When you apply the low-volume exemption, the primary engineering control will be placed in a positive pressure room. The primary engineering control has no impact on this issue. The facility should still address how hazardous drugs are stored. Obviously, in cases where more than true low volumes are prepared, this storage issue creates a real potential for problems.

#### **Vial contamination:**

The outside of the hazardous drug vials are contaminated with the hazardous drugs when they come from the pharmaceutical companies. This has been widely published in the literature. Please see attachment “vial surface contamination”. This problem is going to exist regardless of the primary engineering control used. The challenge of the pharmacy is to ensure that the non-hazardous preparations compounded in this room do not become contaminated with the hazardous drug residue and then track that residue throughout the hospital. I cannot take serious any claim by a manufacturer that states their isolator can make this problem go away. It is simply

irresponsible. The more hazardous drugs prepared in the room, the more this problem becomes. To be honest, I suggest even true low volume facilities create a strategy to deal with this problem.

**External venting:**

The low volume exemption allows the primary engineering control to be vented back into the room as long as the second tier of containment is added (CSTD). There are no exceptions to this regardless what manufacturers will tell you. NIOSH, CETA, USP have all been lobbied by engineering control manufacturers arguing that their products do not need to be externally vented. None of them have bought off on those claims. It is simply fact that particulate hazards such as aerosols are dealt with by HEPA filtration. When the hazard is volatile in nature such as cyclophosphamide and certain other hazardous drugs, the engineering controls must be vented outside the building. Allowances were made for true low volume applications but not for routine compounding operations. In cases where hazardous drugs are compounded daily or for multiple preparations per day, the primary engineering control should be externally vented. This is according to USP, NIOSH, and CETA.

These are just 3 reasons I hope you continue your current policy. When loopholes are left open for manufacturers to provide their own validation, you are at the mercy of their scientific creativity and integrity and that has been found to be lacking too many times. For example, the manufacturer of the turbulent flow isolator cited in the enclosed paper "622 ASHP unidirectional air flow" has many scientific studies conducted and commissioned by themselves proving the isolator to be suitable for sterile compounding. However, when an independent study was conducted, the turbulent flow isolator was found to be inappropriate for sterile work. Certification criteria established by independent organizations are more reliable barometers of right or wrong than the company reliant on the sale of that product. I cannot provide scientific proof that 15 is no good and 14 is okay but the concept that low volume should be reserved for those who do not compound hazardous drugs daily or regularly is sound.

I hope this information is helpful. Please feel free to call me any time if you would like to discuss further.

On another note, I also included a copy of the CETA applications guide "CAG-008-2010" for reviewing a sterile compounding facility certification report. As we discussed, it might be helpful to your inspectors to be able to interpret the certification reports. Let me know if this is of any interest to you.

Best regards,

Jim Wagner  
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Hellertown, PA 18055  
Ph: 484.852.0310  
Cell: 610.428.0371

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**From:** Juran, Caroline (DHP) [<mailto:Caroline.Juran@DHP.VIRGINIA.GOV>]  
**Sent:** Thursday, November 17, 2011 3:27 PM  
**To:** [jimwagner@cenvironment.com](mailto:jimwagner@cenvironment.com)  
**Subject:** "low volume" - Need Assistance  
**Importance:** High

Mr. Wagner,

Thank you so much for speaking with me earlier today. As I mentioned the Board defined "low volume" at the June 2011 full board meeting as no more than 15 compounded hazardous preparations per week or as

defined by USP. As a result, Mr. Hank Rahe, Technical Director, Containment Technologies Group, Inc. submitted information to the Board stating that his company's studies indicate that a much larger volume of hazardous drugs can be compounded safely using a Containment Aseptic Compounding Isolator (CACI) compared to a Class II biological safety cabinet. He offered additional public comment at the September full board meeting, requesting that the Board amend the definition of "low volume" and suggesting the Board place the burden of proof on the manufacturer of the engineering control to state the low-volume benchmark based on independently produced data and studies. The Board voted to refer the request to amend the definition of "low volume" to the regulation committee for further review and for Board staff to obtain any additional information from industry experts for consideration by the committee and full Board. Therefore, I am in the process of seeking additional information from industry experts and as I mentioned to you, Mr. Rick Schnatz with USP suggested I contact you. He indicated that you are a former member of the USP Sterile Compounding Expert Committee and quite knowledgeable in this area. Any information you feel would assist the Board would be greatly appreciated. The committee will meet on November 29<sup>th</sup> from 1pm -5pm at the address below. It is my hope to send an agenda out next week containing information for the Board's consideration.

Thank you for your assistance.

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## Potential for airborne contamination in turbulent- and unidirectional-airflow compounding aseptic isolators

GREGORY F. PETERS, MARGHI R. MCKEON, AND WILLIAM T. WEISS

The emergence of chapter 797 of the *United States Pharmacopeia (USP)*<sup>1</sup> has ushered in the use of compounding aseptic isolators (CAIs) as an alternative to cleanrooms and traditional laminar-airflow workstations (LAFWs) in controlling potential contamination of compounded sterile preparations (CSPs). CAIs are “designed to maintain an aseptic compounding environment (as defined by USP <797>) within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless it has first passed through a microbially retentive filter (HEPA [high-efficiency particulate air] minimum).”<sup>2</sup> Originally termed a “glovebox isolator” or “barrier isolator,” the CAI was introduced into pharmacy CSP operations without the benefit of any objective engineering study to determine its comparative efficacy or superiority in protecting the CSP. Even if practitioners intuit or believe in the potential effectiveness of the

**Purpose.** The ability of turbulent- and unidirectional-airflow compounding aseptic isolators (CAIs) to control airborne contamination during aseptic compounding of compounded sterile preparations (CSPs) was studied.

**Methods.** A three-phase challenge of the comparative airborne-contamination management capabilities of five CAIs was conducted using augmented, industry-standard visual tracer and discrete particle counting methods. In phase 1, a visual smoke tracer was used to conduct a standardized, comparative challenge. In phase 2, CAI operational contamination-control capabilities were measured in accordance with the International Organization for Standardization (ISO) class 5 air cleanliness conditions using a standardized CSP process qualification procedure. Alcohol drying times were also compared. In phase 3, the gross contamination clearance interval required to achieve the ISO class 5 condition after a gross contamination event was measured for each CAI.

**Results.** All four unidirectional-airflow

CAIs met ISO class 5 cleanliness requirements throughout all testing phases and areas of the work zone and demonstrated alcohol drying times of 16 seconds or less. The turbulent-airflow CAI tested failed to achieve the ISO class 5 operating condition at any time during the testing and required alcohol drying times of six minutes. The unidirectional-airflow CAIs tested met the laminar-airflow workstation-equivalency requirements of chapter 797 of the *United States Pharmacopeia*, pharmaceutical aseptic processing standards, the industry-standard definition of a closed isolator, and the rigorous demands of pharmacy and nursing sterile compounding.

**Conclusion.** The performance of four unidirectional-flow CAIs supports their use in pharmacy and nursing CSP operations, whereas the performance of one turbulent-flow CAI does not.

**Index terms:** Air; Aseptic areas; Compounding; Contamination; Control, quality; Equipment; Sterile products

**Am J Health-Syst Pharm.** 2007; 64:622-31

CAI in maintaining an aseptic compounding environment, no minimum standards of CAI design and

use have been validated or adopted in American pharmacy practice. In the absence of such definitive, scientific

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Address correspondence to Mr. Peters at Lab Safety Corporation, 1580 North Northwest Highway, Park Ridge, IL 60068 (valiteq@aol.com).

A relationship, dissolved in February 2006, existed between Valiteq (a division of Lab Safety Corporation) and Scientific Visions (a division of NuAire, Inc., manufacturer of two of the compounding aseptic

isolators [CAIs] tested in this study). The relationship involved Scientific Visions' distribution of Valiteq training literature and media-fill products only and was unrelated to the marketing, sale, or use of CAIs or laminar-airflow workstations (LAFWs). Neither Lab Safety Corporation nor the Mayo Clinic is affiliated with any CAI or LAFW manufacturer or distributor.

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DOI 10.2146/ajhp060067

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cally based knowledge or standards, several CAI designs are being effectively marketed to practitioners.

The purpose of this study was to perform a standardized, uniform assessment of the basic contamination-control performance of various CAIs to assess their ability to support and improve aseptic compounding of CSPs. This study also compared the effectiveness of CAI designs for determining which to use in best practices for pharmacy and nursing CSP compounding operations.

### Background

CAIs currently being marketed to pharmacies incorporate one of two differing internal airborne-contamination management methodologies: unidirectional airflow or turbulent airflow.

**Unidirectional airflow.** Unidirectional airflow (also known as "nonturbulent" or "parallel" airflow) moves "in a single direction in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area."<sup>3</sup> "Laminar airflow," another term for this type of airflow, moves "in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight-line vector."<sup>3</sup> Several minor variations of this definition are recognized; however, all are descriptive of the same condition.<sup>2,4,5</sup> Unidirectional-airflow CAIs control airborne particulate contamination by direct entrainment and removal. Unidirectional airflow is required by the Food and Drug Administration (FDA) as a primary engineering control in critical aseptic processes and in open isolators.<sup>3,6,7</sup> (The unidirectional-airflow CAIs in this study are closed isolators.<sup>2,8</sup> See Appendix A for a glossary.) Qualification of unidirectional airflow in clean spaces requires no more than a 14° divergence from straight-line flow through the work zone.<sup>9</sup> For the purposes of this discussion, the FDA

industry standard definition of unidirectional airflow is used.

**Turbulent airflow.** Turbulent airflow (also known as "nonunidirectional" or "conventional" airflow) is a HEPA-filtered airflow having "multiple-pass circulating characteristics or a nonparallel flow direction."<sup>10</sup> Turbulent airflow is incorporated into CAIs as "the process of introducing a supply of filtered air that mixes with, and dilutes airborne contaminants, thus reducing the concentration within the (controlled) environment."<sup>11</sup> Turbulent airflow is incapable of producing unobstructed, HEPA-filtered supply air ("first air") and "is normally used as secondary or 'buffer' filtration in treating a processing or compounding space which contains laminar-airflow devices to maintain primary critical work surface conditions, or in treating other processing or support areas about which a definitive air-quality statement must be made."<sup>10</sup> In theory, turbulent airflow CAIs control airborne particulate contamination by dilution and dispersion. FDA does not find turbulent airflow acceptable as a primary engineering control in critical aseptic processes, except in certain closed isolators,<sup>3,6,7</sup> wherein all materials placed into the isolator are sterile. This is not the case in pharmacy and nursing practice. The turbulent CAI design tested in this study is undefined; it does not meet the definition of either an open or closed isolator because outside air is introduced into the work zone via its uncontrolled B1 transfer device (antechamber).<sup>2,9,12</sup>

The use of unidirectional airflow in LAFWs to maintain the aseptic compounding field has been the standard of practice in pharmacy since the 1960s. After the inception of USP chapter 797, turbulent-airflow CAIs have been marketed to practitioners as a chapter 797-mandated LAFW equivalent or superior strategy<sup>13</sup> in the elimination and containment of critical work zone airborne

particulate contamination. However, recent concern<sup>14</sup> has emerged about the capability of turbulent airflow to quickly and uniformly remove airborne particulates generated during aseptic compounding that may lead to contamination of critical sites within the aseptic field.<sup>15</sup>

**CAI design perspectives.** Identification of the best CAI operating methodology requires an analysis and a comparison of contamination-management capabilities over both time and space. Because an essential precept in airborne-contamination control is the need to minimize the travel of contaminants, airborne particles generated from nonsterile gloves and gauntlets, syringe wrappers, vials, bags, bottles, and other nonsterile work materials within the aseptic field must be efficiently entrained and removed by process air as quickly as possible. The most efficient designs, therefore, will incorporate the shortest contamination recovery paths and intervals. As a result, both the volume of air exchanged within the CAI and the direction and distance of contaminant travel, determined by the robustness of process air volume and streamlines, become important considerations in effective CAI design. Appropriate CAI operating methodology will not permit recirculation of contaminants within the critical work zone. Using a series of uniform, standardized challenges, this study examines and compares the performance characteristics and capabilities of these two methodologies in controlling airborne contamination during aseptic compounding.

### Study design

In designing a protocol and challenge adequate for the purpose of this study, the operational qualifications contained in the Controlled Environment Testing Association's (CETA's) compounding isolator testing guide<sup>2</sup> were considered. This innovative standard has attempted to provide a schedule of operational

qualifications for the CAI during manufacture, after installation, and periodically thereafter. However, in several instances (e.g., sections 2.01 and 2.08), CETA's operational qualifications defer to the manufacturer's design, implying the suitability of the turbulent-airflow methodology in supporting pharmacy and nursing aseptic compounding practices and allowing manufacturers of turbulent-airflow CAIs to establish special testing criteria for their own designs. Because the turbulent-airflow CAI cannot meet the operating or testing specifications of the unidirectional-airflow CAI, the manufacturer's less-demanding operational qualifications of the turbulent-airflow CAI are deferred to in the CETA standard.

For the purposes of this study, unbiased validation of CAI design methodology through performance relevant to the actual aseptic compounding process was necessary. This required a uniform and objective analysis of CAI performance in the known temporal and spatial constraints of typical pharmacy and nursing compounding operations. Therefore, elements of CETA standard CAG-02-2006 (sections 2.01 and 2.07–2.10) and International Organization for Standardization (ISO) standard 14644-3:1999 (sections 4.2.1, 4.2.5, and 4.2.10) operational qualification challenges, as industry testing standards, were determined to be the appropriate basis of a uniform assessment of CAI performance. To achieve a retrospective qualification of design specific to pharmacy and nursing practice, these challenges required augmentation with enhanced load/no-load particle counting procedures, and incorporation of a surrogate *USP* medium-risk CSP compounding process including (1) actual aseptic work- and waste-streaming practices (Appendix B), (2) normal location and orientation of the CSP's critical orifice (defined as the septum or injection port of

the CSP's finished container during routine aseptic compounding procedures), and (3) routine disinfection of the critical site with isopropyl alcohol.

Because practitioners' CSP compounding techniques and methods would not change according to CAI design methodology, the study (1) was conducted as a uniform, multidimensional assessment, (2) challenged the CAI as the *USP* chapter 797-mandated equivalent of the LAFW, (3) incorporated a robust, worst-case CSP process qualification challenge, (4) embodied realistic concerns about the CSP process, and (5) was applied fairly to each CAI, regardless of design methodology. A three-part challenge was devised to meet these criteria. This challenge was then uniformly conducted, observed, and measured within each CAI included in this study.

**Alcohol disinfection interval: Challenge design.** The CAI represents a new and unique device in the primary engineering control of the CSP process. Because *USP* chapter 797 mandates that the performance of such equipment be equivalent to that of the LAFW, the CAI's operational efficiencies must be compared with those of the LAFW. As a product of CAI airflow management, one such efficiency is the alcohol evaporation rate during surface disinfection. To accomplish a planned disinfection interval, alcohol evaporation characteristics within the workspace of the CAI must be both reasonable and predictable to ensure the maximum plasmolysis of microbial contamination present on and around critical orifices without undue delay of the compounding process. While longer exposure of microorganisms to most disinfectants may increase lethality, complete drying of the alcohol must occur in order to be effective. Due to normal workload, CSP operatives rarely wait if extended periods are required for complete drying of alcohol-saturated critical sites. Fail-

ure to allow the alcohol disinfectant to completely dry on septa and critical work surfaces poses the hazards of both direct viable contamination and alcohol cross-contamination of the end product.<sup>5</sup>

A two-minute exposure time has been shown to produce a 1-log (90%) reduction of bacterial populations,<sup>16,17</sup> and an alcohol disinfection spray-and-wipe procedure has been demonstrated to be superior to spray methods alone.<sup>17</sup> Because best practices in pharmacy for compounding CSPs must be based on realistic operating constraints, an alcohol wipe and two-minute drying procedure is recommended for proper disinfection of work surfaces and critical sites within the CAI.

**CAI selection.** Four unidirectional-airflow CAIs, representing the most widely sold unidirectional designs, were selected for testing: (1) Pharmagard NU-PR797-400 (NuAire, Inc., Plymouth, MN, serial no. 98983052605), (2) Pharmagard NU-SNR797-400 (NuAire, serial no. 103422122205), (3) Germfree LFGI-3USP (Germfree, Inc., Ormond Beach, FL, serial no. 3S-15-LGU-1191), and (4) SterilSHIELD SS 500 (Baker Company, Sanford, ME, serial no. 85693). The turbulent-airflow CAI, representing the most widely sold turbulent design, was selected for testing; it was the mobile isolation chamber (MIC) (Containment Technologies Group [CTG], Indianapolis, IN, serial no. 203-MPA-080). The LAFW reference unit was a model 440-400 type II(A) biological safety cabinet (NuAire, serial no. 83841 AGU).

## Methods

Following successful installation and operational qualifications, one turbulent-flow and four unidirectional-flow CAIs were challenged to compare the two airflow methodologies in removing airborne particulate contamination generated within the aseptic work zone. The

turbulent-flow MIC was challenged in situ at the Gonda Outpatient Procedure Center at the Mayo Clinic in Rochester, Minnesota. All other CAIs challenged in this study incorporated unidirectional airflow and were obtained directly from their manufacturers and installed at the Lab Safety Corporation facility in Cumberland, Wisconsin. The performance analysis

and comparisons of these units were made in a side-by-side configuration (Figure 1). Unit descriptions and manufacturers' design specifications are presented in Table 1. Testing was performed without CTG-approved protocols or training for operation of the MIC.<sup>a</sup>

Internal pressurization of all CAIs in accordance with the manufac-

turer's operating specification was verified by interconnection of a water manometer as a primary standard to each CAI. Manufacturers' data were used to determine CAI process air changes per hour and antechamber purge times. A discrete particle counter (DPC)<sup>b</sup> was located outside the CAI in the normal manner of monitoring (Figure 2), facilitating the sampling of CAI process air, which was then vented outside the main chamber. The DPC was connected to an anisokinetic sampling probe that represented the critical orifice of the final container. The probe was located within the CAI where it would create minimal airflow disturbance. The DPC was installed and operated in accordance with specifications contained in the manufacturer-supplied operator's manual.

All particle counts are expressed as the number of particles  $\geq 0.5 \mu\text{m}$  per cubic foot of air tested ( $\text{p}/\text{ft}^3$ ). The volume of all samples used to calculate ISO cleanliness classes was  $1.0 \text{ ft}^3/\text{min}$ . ISO class 5 (the former FS209e class 100) requires no more than  $100 \text{ p}/\text{ft}^3$  at this particle and sample size. Due to possible interference of the DPC sampling volume of  $1.0 \text{ ft}^3/\text{min}$

**Figure 1.** Configuration of the four unidirectional-flow compounding aseptic isolators (CAIs) during testing. The turbulent-flow CAI is not pictured because it was tested in situ.

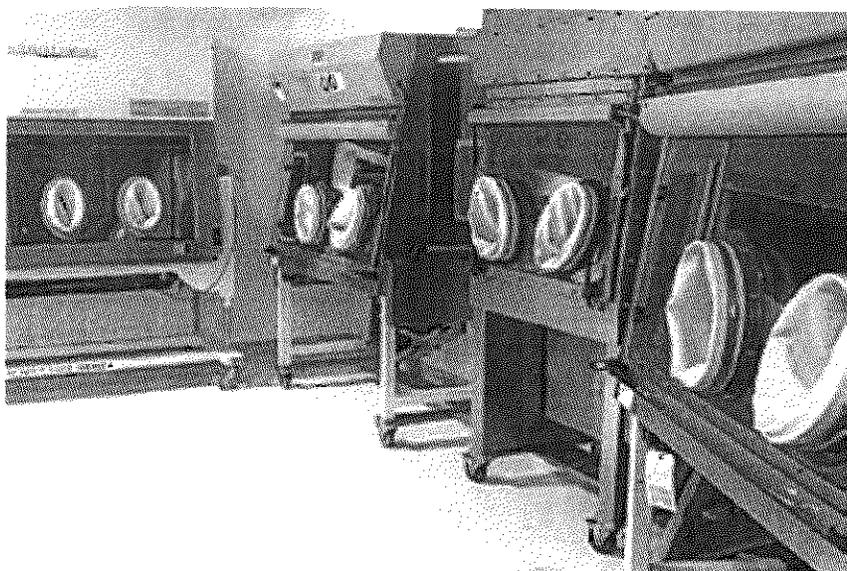


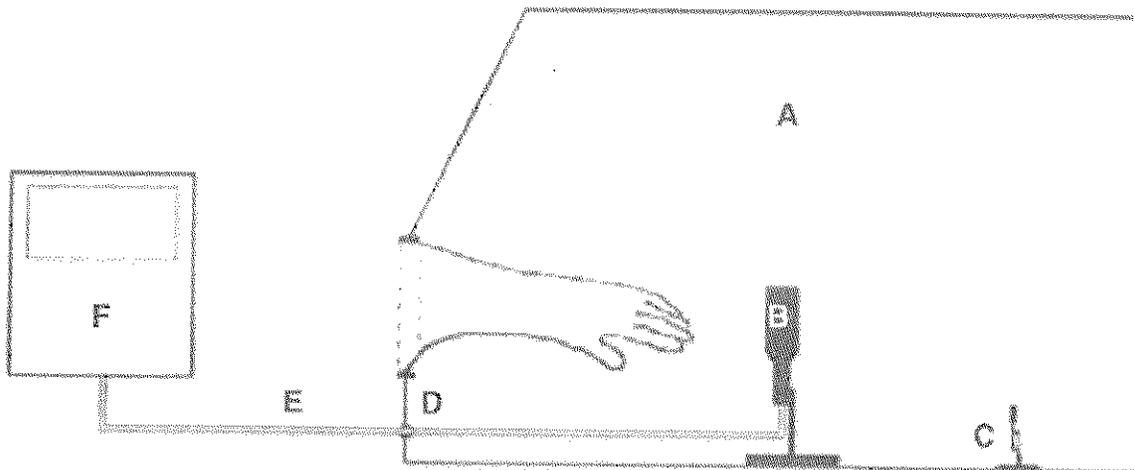
Table 1.  
Compounding Aseptic Isolator Design Characteristics

Device	Unit Pressurized?	Airflow Pattern	No. Supply Air Changes/Hr	Properties		
				Device Pressure Compared with Ambient Pressure (Inches Water Column)		Pass-through Chamber Purge Time (Sec)
				Antechamber	Process Chamber	
Baker SterilSHIELD SS 500	Yes	Unidirectional	792	0.10	0.19	12
Containment Technologies Group mobile isolation chamber	No	Turbulent	200	NA <sup>a</sup>	-0.015	NA
Germfree LFGI-3USP	Yes	Unidirectional	1075	-0.10	0.10	8
NuAire Pharmagard NU-PR797-400	Yes	Unidirectional	1200	0.10	0.20	9
NuAire Pharmagard NU-SNR797-400	No	Unidirectional	1200	-0.15	-0.12	10
NuAire 440-400 (reference unit)	NA	Unidirectional	1800	NA	NA	NA

<sup>a</sup>NA = not applicable.

■ PRACTICE REPORTS Airborne contamination

**Figure 2.** Diagram of a compounding aseptic isolator (CAI). A = process air, B = discrete particle counter (DPC) sampling probe, C = smoke stick, D = pass-through sampling port, E = sampling hose, F = DPC. The DPC was located outside the CAI to facilitate the sampling of process air, which was then vented outside the main chamber.



with the pressurization or airflow characteristics of the MIC CAI (the unit is not designed to make up air volume), the accuracy of 1.0-ft<sup>3</sup>/min samples was verified by examining periodic, random comparison-substitution samples of 0.1 ft<sup>3</sup>.

Where possible, interconnection of the DPC with each CAI was accomplished with a sampling hose passing directly through the gastight exterior test port provided by the manufacturer, terminating at the sampling probe placed at the center of the aseptic field (Figure 2). In the case of the MIC, which lacked a gastight test port, the manufacturer's instructions were followed by (1) removing a waste container from its waste chute, (2) placing the wrist opening of a surgeon's glove over the waste chute opening in a snug elastic fit and securing with a rubber band to form an occlusive seal, (3) puncturing a finger of the glove, and (4) inserting the DPC sampling hose through the finger breach in a snug elastic fit and securing with a rubber band to form an occlusive seal.

In all testing phases, the inlet of the sampling probe was oriented in an upward position 12 in above the critical work surface center to simulate the normal location and proxim-

ity of the CSP critical orifice to the working materials during routine compounding activities. The comparison challenge was performed in three testing phases after establishing at-rest ISO class 5 air cleanliness baselines at the aseptic work surface of each CAI without the presence of a visual smoke tracer, the operator's hands, or surrogate compounding materials.

Testing phase 1: Gross particulate removal challenge. Ten equidistant smoke-test locations within the critical aseptic field of each CAI were identified and mapped (Figure 3). A single, new titanium tetrachloride smoke stick<sup>c</sup> was used to introduce visible and measurable zero-velocity particulates of a size and mass generally equivalent to both airborne microbial and normal atmospheric pyrogenic or nonpyrogenic dust particulates.<sup>18</sup> Introduction of this quiescent tracer was conducted consecutively at each of the 10 test locations to visualize the actual airborne recovery pathways from any work surface or materials where contamination might become aerosolized during routine compounding activities.

The smoke stick was inserted upright into a small, streamlined,

single-wire stand (the assembly). Its cotton reaction matrix was crushed with a plier and held upright to prevent smoke generation. The assembly was introduced normally through the antechamber interface and oriented vertically, placing the point of quiescent smoke emission 4 in above the aseptic work surface (Figures 2 and 3). Orientation of the smoke tracer in this manner simulated and amplified a continuous work-surface-generated particulate contamination source or event at each test location. The assembly was positioned at location 1, and the CAI was allowed to equilibrate for one minute with no work space activity. One hand was inserted into the CAI glove, and the assembly was inverted momentarily to commence the release of the smoke tracer. The tracer was generated continuously during the entire course of phase 1 testing, providing the manufacturer's design quantity<sup>d</sup> of smoke during a one-minute interval at each of the 10 test locations. A five-second interval was then allowed to reposition the assembly at each successive location and retract the gloved hand. The assembly was inverted at three-minute intervals to renew the presence of liquid titanium tetrachloride at the

reaction matrix, ensuring uninterrupted production of the smoke tracer throughout phase 1 testing. During this phase, the DPC was operated continuously, producing a series of consecutive one-minute counts representing a total of 10 ft<sup>3</sup> of air sampled. Values were averaged and analyzed using Gaussian distribution to determine the 95% upper confidence limit (UCL) for the data. The high, low, and 95% UCL particulate contamination values are reported in Table 2. As the visualization component of phase 1 testing, three

individuals observed and recorded the smoke tracer pattern behaviors and airborne recovery pathways.

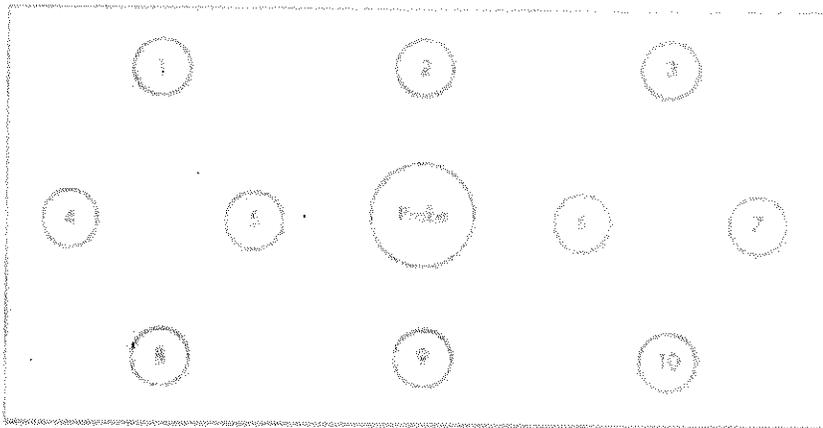
**Testing phase 2: Compounding process qualification.** In order to represent a worst-case, inprocess compounding simulation as a process qualification (PQ) in phase 2, the smoke tracer was removed from the CAI, and surrogate compounding materials were placed onto the critical work surface via the normal antechamber interface. The unit was allowed to equilibrate for one minute with no work activity. The hands of

the operator were then inserted into the gauntlets and engaged in surrogate compounding tasks (Appendix B) as the DPC continuously analyzed 1.0- and 0.1-ft<sup>3</sup>/min process air samples obtained at the surrogate critical orifice (the probe in Figure 2 and 3). The process was monitored by two observers to ensure uniformity and consistency.

Alcohol disinfectant drying times were also established for each type of CAI during phase 2 testing. The humidity and temperature of each CAI work zone were established and recorded using the DPC. Alcohol drying times were then established by placing three 30-mL multidose vials on the center of the aseptic work surface of each CAI. In three individual exercises, each vial was swabbed with a new, premoistened commercial alcohol swab and allowed to dry. The interval required for complete evaporation of the reflective liquid alcohol, as visually determined from each of the vials, was observed and recorded by two observers. The longest single interval was 360 seconds (Table 3).

**Testing phase 3: Contamination clearance interval.** In phase 3, each CAI was filled while inoperative with

**Figure 3.** Smoke-stick test locations (numbers) within the compounding aseptic isolator critical work zone. The probe of the discrete particle counter is in the center and 12 in above the horizontal work surface.



**Table 2.**  
**Compounding Aseptic Isolator Performance Data**

Device	No. 0.5- $\mu$ m Particles/ft <sup>3</sup>						Phase 3: Contaminant Clearance Interval (Sec) (Includes Start- up Interval)
	Phase 1: Gross Particulate Removal Challenge			Phase 2: Compounding Process Qualification			
	95% UCL <sup>a</sup>	Count (Minimum)	Count (Maximum)	95% UCL <sup>a</sup>	Count (Minimum)	Count (Maximum)	
Baker SterilSHIELD SS 500 Containment Technologies Group mobile isolation chamber	19	0	25	8	0	28	70
Germfree LFGI-3U5P	4	0	8	2	0	4	31
NuAire Pharmagard NU- PR797-400	3	0	4	0	0	0	40
NuAire Pharmagard NU- SNR797-400	11	2	13	9	4	12	44
NuAire 440-400 (reference unit)	2	0	3	0	0	0	19

<sup>a</sup>UCL = upper confidence limit.

titanium tetrachloride smoke sufficient to produce a homogeneous visible presence of the tracer throughout the work chamber. The unit was then activated to measure the interval from activation to the achievement of the required ISO class 5 operating condition at the surrogate critical orifice. To prevent damage to the DPC by sampling above the particle counter's coincidence loss rate, the counting procedure did not begin until visible clearance of the tracer was observed. Based on understanding and observation of normal pharmacy process flow and the comparative baseline performance of the reference LAFW (Table 2), an interval of 3.5 minutes was empirically selected as the maximum reasonable process delay for this return-to-equilibrium challenge. Counting was halted after twice that interval (7 minutes) had elapsed or when ISO class 5 conditions were established and confirmed by at least two consecutive counts.

**Results**

**Phase 1. Unidirectional-flow CAIs.** Observation of the tracer behavior during this phase demonstrated direct recovery of the smoke tracer in cohesive, ribbonlike pathways exiting the aseptic work zone via front and rear return grilles and laterally via work surfaces and wall clearances by all unidirectional-airflow CAIs. No diversion, vortices, or reflux of the visible tracer was observed at the work surface. All process air was

quickly and cohesively recovered, with no stratification or "dead spots" observed within the main work chamber. All unidirectional CAIs maintained continuous ISO class 5 conditions at the surrogate critical orifice during introduction of the smoke tracer at all test locations, demonstrating immediate entrainment and exclusion of airborne particulate contamination from the aseptic work zone (Table 2).

**Turbulent-flow CAI.** Observation of the tracer behavior in the turbulent-flow CAI demonstrated roiling reflux of the smoke tracer throughout the aseptic work zone, resulting in immediate airborne particulate contamination present at the surrogate critical orifice. This contamination remained visually present and measurable outside ISO class 5 conditions for over seven minutes after removal of the smoke source, with several dead spots and air stagnation observed within the main work chamber. At no time during phase 1 testing did the turbulent CAI tested achieve an ISO class 5 operating condition at the critical orifice.

**Phase 2. Unidirectional-flow CAIs.** During phase 2, all unidirectional-flow CAIs maintained continuous ISO class 5 conditions throughout the surrogate CSP compounding process, demonstrating immediate exclusion of airborne particulate contamination from the CSP critical orifice during compounding procedures (Table 2).

**Turbulent-flow CAI.** The turbulent-flow CAI continuously exhibited ISO class 6 and 7 levels of airborne particulate contamination at the critical orifice during the CSP compounding procedures. At no time during phase 2 testing did the turbulent CAI achieve an ISO class 5 operating condition at the critical orifice. The average particle count for the turbulent-flow CAI in this phase was 1520 p/ft<sup>3</sup>, with a 95% UCL of 2735 p/ft<sup>3</sup>. (The minimum particle count recorded at the surrogate critical orifice during this phase was 128 p/ft<sup>3</sup> [ISO class 6], while the maximum was 9978 p/ft<sup>3</sup> [ISO class 7].)

**Alcohol disinfection interval challenge. Unidirectional-flow CAIs.** Alcohol drying times of ≤16 seconds were observed for all unidirectional-flow CAIs tested.

**Turbulent-flow CAI.** Alcohol drying times of six minutes were observed in the turbulent-flow CAI tested. When controlling for variation in internal operating temperature and humidity, evaporation time in the turbulent-flow CAI would not be expected to be more than 150% of the evaporation time in the unidirectional-flow CAI.<sup>c</sup>

**Phase 3. Unidirectional-flow CAIs.** The gross airborne contamination clearance interval to an ISO class 5 operating condition observed for the unidirectional-flow CAIs ranged from 31 to 70 seconds (Table 2).

**Turbulent-flow CAI.** The gross airborne contamination clearance

Table 3. Compounding Aseptic Isolator Temperature, Relative Humidity, and Alcohol Drying Time

Device	Average Temperature (°F)	Average Relative Humidity (%)	Alcohol Dry Time (Sec)
Baker SterilSHIELD SS 500 Containment Technologies Group mobile Isolation chamber	66.5	29.3	16
Germfree LFGI-3USP	70.3	53.8	360
NuAire Pharmagard NU-PR797-400	67.5	30.0	14
NuAire Pharmagard NU-SNR797-400	76.4	53.3	16
NuAire 440-400 (reference unit)	67.4	29.4	15
	71.8	46.4	15

interval observed for the turbulent-flow CAI tested exceeded seven minutes. Counting procedures were halted after seven minutes without achieving ISO class 5 operating conditions.

### Discussion

The results suggest the suitability of the unidirectional-flow CAIs and the unsuitability of the turbulent-flow CAI for use in pharmacy and nursing CSP compounding practices.

Observation of the visual tracer introduced into all unidirectional-flow CAIs tested during phase 1 demonstrated "airflow moving in a single direction in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area,"<sup>23</sup> while observation of the visual tracer in the turbulent-flow CAI demonstrated sluggish, multipass airflow moving in no discernible direction that failed to clear from the unit over extended periods of time. This appears to be due to the considerable reduction in supply airflow cohesiveness and volume within the turbulent-flow CAI, calculated at less than 25% of the average supply airflow of the unidirectional-flow CAIs tested and one ninth of the supply airflow of the *USP* chapter 797-mandated reference LAFW tested (Table 2). While the unidirectional-flow CAIs effectively entrained and removed contaminants from the aseptic work zone, the turbulent-flow CAI recirculated contaminants within the aseptic work zone without timely and effective entrainment and removal. Phase 2 particle counts obtained in the turbulent-flow CAI during the PQ were greater than 300 times the highest level of the unidirectional-flow CAIs in both the positive- and negative-pressure configurations. Despite care and uniformity in the conduct of all testing procedures, at no time during testing phases 1, 2, or 3 was an ISO class 5 operating condition achieved in the turbulent-flow CAI tested.

In addition, the turbulent CAI tested did not include a D1 or D2 transfer device<sup>12</sup> (antechamber HEPA-purge feature), essential to the elimination of extraneous airborne particulates that may remain in close proximity to nonsterile compounding materials and be introduced into the aseptic work zone during pass-through, particularly in operations conducted outside an ISO class 7 cleanroom. The B1 transfer device<sup>12</sup> (non-HEPA-purged antechamber) and reduced internal airflow velocities demonstrated in the turbulent-flow CAI may have contributed to the introduction and settling of airborne particulate contamination onto aseptic work surfaces and critical sites, rather than eliminating this type of contamination within the air stream, thus increasing the potential for contamination of the end product.

A controversy currently exists as to whether the CAI should be used within or outside a controlled clean space. This study demonstrated that the tested unidirectional-flow CAIs are as effective as traditional LAFWs in maintaining operational ISO class 5 conditions at the CSP critical orifice (Tables 2 and 3). Internal airborne particulate levels were controlled within an ISO class 5 condition when supplies were properly precleaned and introduced via a D1 or D2 transfer device (HEPA-purged antechamber) by a gowned operator in an ISO class 8 environment. However, a wide range of outside environments and operating procedures exist. An ungowned operator or an excessively dirty external environment is likely to substantially increase the contamination burden on working materials. It must, therefore, be assumed that there is some level of external contamination that will negatively impact end-product quality. Because this study did not address the effects of CAIs operating under worst-case environmental conditions, the possible negative impact of a B1 transfer device (non-HEPA-purged ante-

chamber) on the aseptic work zone, improper precleaning of working materials, and improper operator gowning, no recommendation can be made for CAI operation outside a controlled ISO class 8 environment or for elimination of the use of a gown, hair cover, mask, and shoe covers.

As a factor in realistic CSP process design and execution, the alcohol disinfectant drying times observed in the turbulent-flow CAI are excessive to the point of either causing undue delay of the process or encouraging premature resumption of the process before complete drying, and the maximum plasmolysis of potential viable surface contaminants can occur. Neither scenario is acceptable in terms of customary pharmacy workload or patient safety.

The unidirectional-flow CAIs tested rapidly and reliably entrained and removed large quantities of airborne particulate contamination from the aseptic work zone, provided first air to the working materials, and facilitated the rapid drying of alcohol surface disinfectant. In addition, all unidirectional-flow CAIs tested incorporated a D1 or D2 antechamber HEPA-purge feature to eliminate airborne contaminants before the introduction of nonsterile working materials into the aseptic work area. These attributes constitute best practices and are necessary to support the aseptic compounding process in pharmacy and nursing CSP operations in accordance with closed isolator design and testing standards.<sup>2,8</sup> In clear contrast, the unclassified turbulent-flow CAI did not exhibit any of these attributes. The turbulent-flow CAI could allow for a higher airborne contamination burden for process air within the critical compounding area resulting from its lack of robust and efficient process airflow and from the absence of a D1 or D2 antechamber HEPA-purge feature. This increases the risk that viable contamination will reach the patient, leading to a

higher rate of pharmacy- and nursing-induced infections, compared with unidirectional-flow CAIs possessing both robust process airflow and a D1 or D2 HEPA-purged antechamber.<sup>2,8,11</sup>

The unidirectional-flow CAIs tested met the LAFW-equivalency requirements of USP chapter 797, pharmaceutical aseptic processing standards,<sup>3,6,7</sup> the industry-standard definition of a closed isolator,<sup>4,8,16</sup> and the rigorous demands of pharmacy and nursing sterile compounding. The unidirectional-flow CAIs tested will support the optimum alcohol disinfection routine. In view of these findings, the unidirectional-flow design methodology is recommended for CAIs used in pharmacy and nursing CSP operations.

The unclassified turbulent-flow CAI tested did not meet the LAFW-equivalency requirements of USP chapter 797 or pharmaceutical aseptic processing standards, the definition of a CAI,<sup>9,11</sup> the industry-standard definition of an open or closed isolator, or the rigorous demands of pharmacy and nursing CSP operations. Neither did the turbulent-flow CAI tested support the optimum alcohol disinfection routine. In view of these findings, the tested turbulent-flow CAI cannot be recommended for use in pharmacy and nursing CSP operations.

### Conclusion

The performance of four unidirectional-flow CAIs supports their use in pharmacy and nursing CSP operations, whereas the performance of one turbulent-flow CAI does not.

<sup>a</sup>According to CTG, "The MICs have unidirectional airflow in the critical zone of compounding" (CTG advertising claim, *Am J Health-Syst Pharm*. 2005; 62:2577), but this is not supported by industry standards or generally accepted engineering control principles. CTG declined to provide (1) an MIC unit for testing, (2) proprietary MIC operating and sterilization protocols, or (3) proprietary studies supporting the MIC unit's design and operational qualifications.

<sup>b</sup>Climet CI-500 discrete particle counter/probe (sample rate, 1 ft<sup>3</sup>/min), Climet Instruments, Red-

lands, CA, serial 999558. This unit was calibrated to a National Institute of Standards and Technology-traceable standard within the previous six months.

<sup>c</sup>Tel-Tru Smoke Sticks, E. Vernon Hill, Benicia, CA, product 15-049.

<sup>d</sup>The titanium tetrachloride smoke stick produces a concentration of particles at the matrix source too numerous to count without further air dilution. DPC enumeration of particulates within the work space becomes possible only after source particles become entrained within the process airstream and dilution of the source concentration occurs. The smoke sticks employed in this test exhibited the usual and customary visual concentration of particulates at all times until exhaustion one to two minutes after completing each test. The geometric number average diameter of the particles was 0.13–0.35 μm (manufacturer's data).

<sup>e</sup>Evaporation rate is also affected by air movement and other factors. The extended drying times and elevated relative humidity observed within the turbulent-flow CAI tested appear to be the result of a totally closed system with no design exhaust or makeup air, inhibiting vapor dilution. Temperature and relative humidity are the two prominent factors affecting evaporation. Higher temperatures increase the evaporation rate ( $R_e$ ), while higher elevated humidity has the reverse effect. Temperature differences in this study were negligible. When time fluctuation is ignored, the formula to measure the effect of relative humidity on evaporation becomes  $R_e = 1 - \text{relative humidity}/100$  ([www.newton.dep.anl.gov](http://www.newton.dep.anl.gov)). (The average relative humidity in the MIC unit was 53%, while the lowest average relative humidity in the unidirectional-flow CAI units tested was 29%.) Using this formula, we calculated the comparative  $R_e$  in the MIC to be 0.47, while the highest comparative  $R_e$  was 0.71; therefore, the highest comparative  $R_e$  was 1.5 times the  $R_e$  observed in the MIC unit. (These calculations determine only the effect of relative humidity in this study, not the absolute  $R_e$  of 70% isopropyl alcohol.)

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### Appendix A—Glossary of terms

**Anisokinetic probe:** Air sampling probe inlet velocities unequal to unidirectional probe inlet velocities in unidirectional-flow CAIs; probe diameter uncorrectable for isokinesis at reduced CAI velocities of 40–50 lpm.

**At rest:** Engineering controls and equipment operating at idle, with no operator or working materials present.

**Best-case:** A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures that pose the least chance of process or product failure compared with worst-case conditions. Such conditions do not necessarily ensure product safety or efficacy.

**Buffer zone:** An enclosed, controlled-access aseptic processing room area housing LAFWs as primary engineering controls. Also known as the "core." USP chapter 797 requires that CSP process buffer zones be maintained at ISO class 7 (former FS209e class 10,000).

**Closed isolator:** A positively or negatively pressurized isolator that excludes contaminants from the critical work zone by accomplishing material transfer through a D1 or D2 transfer device rather than through direct openings to the surrounding environment or an uncontrolled transfer device. A closed isolator will exclude transfer of untreated room air either directly or indirectly to the main chamber.

**CSP critical orifice:** The septum or injection port of a CSP's finished container and its orientation during routine aseptic compounding procedures.

**Installation qualification:** Systematic documentary evidence that a facility or device is installed and finished in accordance with design and process parameters or manufacturer's specifications.

**ISO class 5:** Air containing no more than 100 p/ft<sup>3</sup> that are 0.5 µm or larger in diameter (3520 p/m<sup>3</sup>); formerly FS209e class 100.

**ISO class 6:** Air containing no more than 1000 p/ft<sup>3</sup> that are 0.5 µm or larger in diameter (35,200 p/m<sup>3</sup>); formerly FS209e class 1,000.

**ISO class 7:** Air containing no more than 10,000 p/ft<sup>3</sup> that are 0.5 µm or larger in diameter (352,000 p/m<sup>3</sup>); formerly FS209e class 10,000.

**Open isolator:** A positively pressurized isolator designed to allow the ingress and egress of working materials through one or more direct openings to the room during operations. Open isolators do not allow the exchange of unfiltered air or contaminants with adjacent environments.

**Operational qualification:** Systematic documentary evidence that a facility or device is capable of repeatedly and reliably operating within design and process parameters or manufacturer's specifications.

**Performance qualification:** Systematic documentary evidence that an aseptic process is capable of repeatedly and reliably producing a finished product of the required quality.

**Plasmolysis:** Shrinkage or contraction of

the protoplasm away from the wall of a plant or bacterial cell. Death of the isopropyl or ethyl alcohol-saturated bacterial cell is caused by drying of the alcohol and the resulting loss of water through osmosis.

**Primary engineering control:** An air handling device used to control air quality in the critical work zone of the aseptic process.

**Primary standard:** A reference standard that directly quantifies a measurand without the need for conversion or calibration (i.e., calibration of secondary electromechanical methods in the measurement of pressure, temperature, or other attributes, such as magnehelic or digital pressure gauges or thermocouples); a standard to which secondary standards or measurement devices are calibrated.

**Process air:** Controlled airflow being supplied to, and removed from, the aseptic work zone of the CAI for maintenance of required ISO class 5 in-process cleanliness condition.

**Process qualification:** Following the design, installation, and operational qualifications of the compounding facility and comprehensive training and verification of the aseptic technique of CSP operatives, the process qualification exercise is a simulation of the actual, finished compounding process using surrogate compounding materials under actual compounding conditions (known in industry as a "qual run." Several "prequal runs" may be necessary to establish a satisfactory process). Based on the results of physical measurements (i.e., particle counts, microbial monitoring, temperature, and humidity) and observations documented during the exercise confirming operation within predetermined process design parameters, a successful outcome of the process qualification may then be represented to a regulatory group as a qualification of the adequacy of the process.

**Secondary engineering control:** An air handling device used to control air quality in the anteroom and buffer zones of the aseptic process.

**Surrogate compounding exercise:** A 15-step, worst-case, observed demonstration of the nine, basic USP medium-risk core aseptic techniques employing all necessary drug containers with sterile, microbiological growth medium manipulated in place of the actual drug. Successful outcome of this challenge requires that all simulated end products remain sterile following admixture and incubation. In combination with the proctor-observed successful assessment of aseptic technique, the surrogate compounding exercise verifies the candidate's ability to safely and accurately compound CSPs.

**Worst-case:** A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures that pose the greatest chance of process or product failure when compared with ideal or best-case conditions. Such conditions do not necessarily induce product or process failure.

## Appendix B—Aseptic work- and waste-streaming practices

A uniform surrogate USP medium-risk compounding process incorporating a commercial piggyback bag containing 100 mL of 0.9% sodium chloride injection, 10-mL and 60-mL syringes, 21-gauge needles, a filter needle, a 10-mL single-dose vial containing liquid, a 30-mL multidose vial containing liquid, a 20-mL multidose vial containing powder for reconstitution, a 10-mL ampul containing liquid, and prepackaged 70% alcohol swabs.

### 15-Step procedure

1. Preclean supplies with a 70% alcohol wipe.
2. Stage the working materials in the antechamber.
3. Follow manufacturer's instructions for introduction into the work chamber and for work zone equilibration. Use identical type and range of aseptic manipulations for each challenge (steps 4 through 15).
4. Disinfect gloves and gauntlets.
5. Assemble all syringes and needles.
6. Dispose of all wrappers and debris using the CAI pass-through waste facility.
7. Resanitize the work and glove surfaces.
8. Disinfect all septa and ports with separate alcohol swabs.
9. Allow the CAI to equilibrate for one minute and allow alcohol to dry before commencing compounding activities.
10. Remove 50 mL of 0.7% sodium chloride injection from 100-mL piggyback and reconstitute sterile powder with 20 mL of 0.7% sodium chloride injection. Discard remaining 0.7% sodium chloride injection.
11. Withdraw three 5-mL samples from the 30-mL multidose vial and add to piggyback.
12. Withdraw three 5-mL samples of reconstituted sterile powder and add to piggyback.
13. Withdraw 10 mL from the 10-mL single-dose vial and add to piggyback.
14. Withdraw 10 mL from the 10-mL ampul and add to piggyback. Swirl piggyback gently to mix.
15. Stage in antechamber for removal.

## ASHP Guidelines on Handling Hazardous Drugs

In 1990, the American Society of Health-System Pharmacists (ASHP) published its revised technical assistance bulletin (TAB) on handling cytotoxic and hazardous drugs.<sup>1</sup> The information and recommendations contained in that document were current to June 1988. Continuing reports of workplace contamination and concerns for health care worker safety prompted the Occupational Safety and Health Administration (OSHA) to issue new guidelines on controlling occupational exposure to hazardous drugs in 1995.<sup>2,3</sup> In 2004, the National Institute for Occupational Safety and Health (NIOSH) issued the "NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings."<sup>4</sup> The following ASHP Guidelines on Handling Hazardous Drugs include information from these recommendations and are current to 2004.

### Purpose

The purpose of these guidelines is to (1) update the reader on new and continuing concerns for health care workers handling hazardous drugs and (2) provide information on recommendations, including those regarding equipment, that have been developed since the publication of the previous TAB. Because studies have shown that contamination occurs in many settings, these guidelines should be implemented wherever hazardous drugs are received, stored, prepared, administered, or disposed.<sup>2-7</sup>

Comprehensive reviews of the literature covering anecdotal and case reports of surface contamination, worker contamination, and risk assessment are available from OSHA,<sup>2,3</sup> NIOSH,<sup>4</sup> and individual authors.<sup>5-7</sup> The primary goal of this document is to provide recommendations for the safe handling of hazardous drugs.

These guidelines represent the recommendations of many groups and individuals who have worked tirelessly over decades to reduce the potential harmful effects of hazardous drugs on health care workers. The research available to date, as well as the opinions of thought leaders in this area, is reflected in the guidelines. Where possible, recommendations are evidence based. In the absence of published data, professional judgment, experience, and common sense have been used.

### Background

Workers may be exposed to a hazardous drug at many points during its manufacture, transport, distribution, receipt, storage, preparation, and administration, as well as during waste handling and equipment maintenance and repair. All workers involved in these activities have the potential for contact with uncontained drug.

Early concerns regarding the safety of workers handling potentially hazardous drugs focused on antineoplastic drugs when reports of second cancers in patients treated with these agents were coupled with the discovery of mutagenic substances in nurses who handled these drugs and cared for treated patients.<sup>8,9</sup> Exposure to these drugs in the workplace has been associated with acute and short-term reactions,

as well as long-term effects. Anecdotal and case reports in the literature range from skin-related and ocular effects to flu-like symptoms and headache.<sup>4,5,10-17</sup> Two controlled surveys have reported significant increases in a number of symptoms, including sore throat, chronic cough, infections, dizziness, eye irritation, and headaches, among nurses, pharmacists, and pharmacy technicians routinely exposed to hazardous drugs in the workplace.<sup>18,19</sup> Reproductive studies on health care workers have shown an increase in fetal abnormalities, fetal loss, and fertility impairment resulting from occupational exposure to these potent drugs.<sup>20-23</sup> Antineoplastic drugs and immunosuppressants are some of the types of drugs included on lists of known or suspected human carcinogens by the National Toxicology Program<sup>24</sup> and the International Agency for Research on Cancer.<sup>25</sup> Although the increased incidence of cancers for occupationally exposed groups has been investigated with varying results,<sup>26,27</sup> a formal risk assessment of occupationally exposed pharmacy workers by Sessink et al.<sup>28</sup> estimated that cyclophosphamide causes an additional 1.4–10 cases of cancer per million workers each year. This estimate, which considered workplace contamination and worker contamination and excretion in combination with animal and patient studies, was based on a conservative exposure level. Connor et al.<sup>29</sup> found greater surface contamination in a study of U.S. and Canadian clinical settings than had been reported in European studies conducted by Sessink and colleagues.<sup>30-32</sup> Ensslin et al.<sup>33</sup> reported an almost fivefold greater daily average excretion of cyclophosphamide in their study than that reported by Sessink. These later findings could add 7–50 additional cancer cases per year per million workers to Sessink's estimate. From these and other studies that show variations in work practices and engineering controls,<sup>34,35</sup> it may be assumed that such variations contribute to differences in surface and worker contamination.

**Routes of Exposure.** Numerous studies showed the presence of hazardous drugs in the urine of health care workers.<sup>30-34,36-41</sup> Hazardous drugs enter the body through inhalation, accidental injection, ingestion of contaminated foodstuffs or mouth contact with contaminated hands, and dermal absorption. While inhalation might be suspected as the primary route of exposure, air sampling studies of pharmacy and clinic environments have often demonstrated low levels of or no airborne contaminants.<sup>30-32,40</sup> Recent concerns about the efficacy of the sampling methods<sup>42</sup> and the possibility that at least one of the marker drugs may be volatile<sup>42-45</sup> and thus not captured on the standard sampling filter leave the matter of inhalational exposure unresolved. Surface contamination studies do, however, suggest that dermal contact and absorption may be a primary route of exposure.<sup>31,46</sup> While some hazardous drugs are dermally absorbed, a 1992 report showed no detectable skin absorption of doxorubicin, daunorubicin, vincristine, vinblastine, or melphalan.<sup>47</sup> An alternative to dermal absorption is that surface contamination transferred to hands may be ingested via the hand-to-mouth route.<sup>48,49</sup> One or more of these routes might be responsible for workers' exposure.

**Hazard Assessment.** The risk to health care personnel from handling hazardous drugs is the result of a combination of the inherent toxicity of the drugs and the extent to which workers are exposed to the drugs in the course of their daily job activities. Both hazard identification (the qualitative evaluation of the toxicity of a given drug) and an exposure assessment (the amount of worker contact with the drug) are required to complete a hazard assessment. As the hazard assessment is specific to the safety program and safety equipment in place at a work site, a formal hazard assessment may not be available for most practitioners. An alternative is a performance-based, observational approach. Observation of current work practices, equipment, and the physical layout of work areas where hazardous drugs are handled at any given site will serve as an initial assessment of appropriate and inappropriate practices.<sup>4</sup>

### Hazardous Drugs as Sterile Preparations

Many hazardous drugs are designed for parenteral administration, requiring aseptic reconstitution or dilution to yield a final sterile preparation. As such, the compounding of these products is regulated as pharmaceutical compounding by the *United States Pharmacopeia (USP)*, chapter 797.<sup>50</sup> The intent of chapter 797 is to protect patients from improperly compounded sterile preparations by regulating facilities, equipment, and work practices to ensure the sterility of extemporaneously compounded sterile preparations. Chapter 797 addresses not only the sterility of a preparation but also the accuracy of its composition. Because many hazardous drugs are very potent, there is little margin for error in compounding.

The initial version of chapter 797, released in early 2004, provided only minimal guidance for the handling of hazardous drugs, limiting this issue to a short discussion of chemotoxic agents in the document's section on aseptic technique. The chapter referred to standards established by the International Organization for Standardization (ISO)<sup>51</sup> that address the acceptable air quality (as measured by particulate counts) in the critical environment but failed to discuss airflow, air exchanges per hour, or pressure gradients of the ISO standards for cleanrooms and associated environments for compounding sterile products. The chapter did not describe the containment procedures necessary for compounding sterile hazardous agents, leaving it to the practitioner to simultaneously comply with the need to maintain a critical environment for compounded sterile products for patient safety while ensuring a contained environment for worker safety. The use of positive-pressure isolators for compounding hazardous drugs or placement of a Class II biological-safety cabinet (BSC) for use with hazardous drugs in a positive-pressure environment may result in airborne contamination of adjacent areas. Engineering assessment of designs of areas where this may occur should be done to address concerns of contaminant dissemination. Because hazardous drugs are also compounded in areas adjacent to patients and their family members (e.g., in chemotherapy infusion centers), inappropriate environmental containment puts them, as well as health care workers, at risk. Because *USP* review is a dynamic and ongoing process, future revisions are likely to address these concerns. Practitioners are encouraged to monitor the process and participate when appropriate.

### Definition of Hazardous Drugs

The federal hazard communication standard (HCS) defines a hazardous chemical as any chemical that is a physical or health hazard.<sup>52,53</sup> 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. The HCS further notes that the term *health hazard* includes chemicals that are carcinogens, toxic or highly toxic agents, reproductive toxins, irritants, corrosives, sensitizers, and agents that produce target organ effects.

A 1990 ASHP TAB proposed criteria to determine which drugs should be considered hazardous and handled within an established safety program.<sup>1</sup> OSHA adopted these criteria in its 1995 guidelines, which were posted on its Web site in 1999.<sup>2,3</sup> The TAB's definition of hazardous drugs was revised by the NIOSH Working Group on Hazardous Drugs for the 2004 alert.<sup>4</sup> These definitions are compared in Table 1.

Each facility should create its own list of hazardous drugs based on specific criteria. Appendix A of the NIOSH alert contains related guidance and a sample list.<sup>4</sup> When drugs are purchased for the first time, they must be evaluated to determine whether they should be included in the facility's list of hazardous drugs. As the use and number of hazardous drugs increase, so too do the opportunities for health care worker exposure. Investigational drugs must be evaluated according to the information provided to the principal investigator. If the information provided is deemed insufficient to make an informed decision, the investigational drug should be considered hazardous until more information is available.

### Recommendations

**Safety Program.** Policies and procedures for the safe handling of hazardous drugs must be in place for all situations in which these drugs are used throughout a facility. A comprehensive safety program must be developed that deals with all aspects of the safe handling of hazardous drugs. This program must be a collaborative effort, with input from all affected departments, such as pharmacy, nursing, medical staff, housekeeping, transportation, maintenance, employee health, risk management, industrial hygiene, clinical laboratories, and safety. A key element of this safety program is the Material Safety Data Sheet (MSDS) mandated by the HCS.<sup>52,53</sup> Employers are required to have an MSDS available for all hazardous agents in the workplace. A comprehensive safety program must include a process for monitoring and updating the MSDS database. When a hazardous drug is purchased for the first time, an MSDS must be received from the manufacturer or distributor. The MSDS should define the appropriate handling precautions, including protective equipment, controls, and spill management associated with the drug. Many MSDSs are available online through the specific manufacturer or through safety-information services.

Drugs that have been identified as requiring safe handling precautions should be clearly labeled at all times during their transport and use. The HCS applies to all workers, including those handling hazardous drugs at the manufac-

Table 1.  
Comparison of 2004 NIOSH and 1990 ASHP Definitions of Hazardous Drugs<sup>a</sup>

NIOSH <sup>4</sup>	ASHP <sup>1</sup>
Carcinogenicity	Carcinogenicity in animal models, in the patient population, or both as reported by the International Agency for Research on Cancer
Teratogenicity or developmental toxicity <sup>b</sup>	Teratogenicity in animal studies or in treated patients
Reproductive toxicity <sup>b</sup>	Fertility impairment in animal studies or in treated patients
Organ toxicity at low doses <sup>b</sup>	Evidence of serious organ or other toxicity at low doses in animal models or treated patients
Genotoxicity <sup>c</sup>	Genotoxicity (i.e., mutagenicity and clastogenicity in short-term test systems)
Structure and toxicity profile of new drugs that mimic existing drugs determined hazardous by the above criteria	

<sup>a</sup>NIOSH = National Institute for Occupational Safety and Health, ASHP = American Society of Health-System Pharmacists.

<sup>b</sup>NIOSH's definition contains the following explanation: "All drugs have toxic side effects, but some exhibit toxicity at low doses. The level of toxicity reflects a continuum from relatively nontoxic to production of toxic effects in patients at low doses (for example, a few milligrams or less). For example, a daily therapeutic dose of 10 mg/day or a dose of 1 mg/kg/day in laboratory animals that produces serious organ toxicity, developmental toxicity, or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 micrograms/meter<sup>3</sup> after applying appropriate uncertainty factors. OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry. Under all circumstances, an evaluation of all available data should be conducted to protect health care workers."

<sup>c</sup>NIOSH's definition contains the following explanation: "In evaluating mutagenicity for potentially hazardous drugs, responses from multiple test systems are needed before precautions can be required for handling such agents. The EPA evaluations include the type of cells affected and *in vitro* versus *in vivo* testing."

turer and distributor levels. Employers are required to establish controls to ensure worker safety in all aspects of the distribution of these drugs.

The outside of the vials of many commercial drugs are contaminated by the time they are received in the pharmacy.<sup>30,54,55</sup> Although the possibility has not been studied, the contamination may extend to the inside of the packing cartons and onto the package inserts placed around the vial within the carton. Such contamination would present an exposure risk to anyone opening drug cartons or handling the vials, including workers receiving open or broken shipping cartons or selecting vials to be repackaged at a distribution point (e.g., a worker at the drug wholesaler selecting hazardous drugs for shipping containers or a pharmacy worker dividing a hazardous drug in a multidose container for repackaging into single-dose containers). These activities may present risks, especially for workers who too often receive inadequate safety training. Housekeepers and patient care assistants who handle drug waste and patient waste are also at risk and are not always included in the safe handling training required by safety programs. Safety programs must identify and include all workers who may be at risk of exposure.

The packaging (cartons, vials, ampuls) of hazardous drugs should be properly labeled by the manufacturer or distributor with a distinctive identifier that notifies personnel receiving them to wear appropriate personal protective equipment (PPE) during their handling. Sealing these drugs in plastic bags at the distributor level provides an additional level of safety for workers who are required to

unpack cartons. Visual examination of such cartons for outward signs of damage or breakage is an important first step in the receiving process. Policies and procedures must be in place for handling damaged cartons or containers of hazardous drugs (e.g., returning the damaged goods to the distributor using appropriate containment techniques). These procedures should include the use of PPE, which must be supplied by the employer. As there may be no ventilation protection in the area where damaged containers are handled, the use of complete PPE, including an NIOSH-certified respirator, is recommended.<sup>56,57</sup> As required by OSHA, a complete respiratory program, including proper training and fit testing, must be completed by all staff required to use respirators.<sup>56</sup> Surgical masks do not provide adequate protection from the harmful effects of these drugs.

*Labeling and Packaging from Point of Receipt.* Drug packages, bins, shelves, and storage areas for hazardous drugs must bear distinctive labels identifying those drugs as requiring special handling precautions.

Segregation of hazardous drug inventory from other drug inventory improves control and reduces the number of staff members potentially exposed to the danger. Hazardous drugs should be stored in an area with sufficient general exhaust ventilation to dilute and remove any airborne contaminants.<sup>4</sup> Hazardous drugs placed in inventory must be protected from potential breakage by storage in bins that have high fronts and on shelves that have guards to prevent accidental falling. The bins must also be appropriately sized to properly contain all stock. Care should be taken to separate hazardous drug inventory to reduce potential drug errors (e.g., pulling a look-alike vial from an adjacent drug bin). Because studies have shown that contamination on the drug vial itself is a consideration,<sup>30,54,55</sup> all staff members must wear double gloves when stocking and inventorying these drugs and selecting hazardous drug packages for further handling. All transport of hazardous drug packages must be done in a manner to reduce environmental contamination in the event of accidental dropping. Hazardous drug packages must be placed in sealed containers and labeled with a unique identifier. Carts or other transport devices must be designed with guards to protect against falling and breakage. All individuals transporting hazardous drugs must have safety training that includes spill control and have spill kits immediately accessible. Staff handling hazardous drugs or cleaning areas where hazardous drugs are stored or handled must be trained to recognize the unique identifying labels used to distinguish these drugs and areas. Warning labels and signs must be clear to non-English readers. All personnel

who work with or around hazardous drugs must be trained to appropriately perform their jobs using the established precautions and required PPE.<sup>52</sup>

**Environment.** Hazardous drugs should be compounded in a controlled area where access is limited to authorized personnel trained in handling requirements. Due to the hazardous nature of these preparations, a contained environment where air pressure is negative to the surrounding areas or that is protected by an airlock or anteroom is preferred. Positive-pressure environments for hazardous drug compounding should be avoided or augmented with an appropriately designed antechamber because of the potential spread of airborne contamination from contaminated packaging, poor handling technique, and spills.

Only individuals trained in the administration of hazardous drugs should do so. During administration, access to the administration area should be limited to patients receiving therapy and essential personnel. Eating, drinking, applying makeup, and the presence of foodstuffs should be avoided in patient care areas while hazardous drugs are administered. For inpatient therapy, where lengthy administration techniques may be required, hanging or removing hazardous drugs should be scheduled to reduce exposure of family members and ancillary staff and to avoid the potential contamination of dietary trays and personnel.

Because much of the compounding and administration of hazardous drugs throughout the United States is done in outpatient or clinic settings with patients and their family members near the compounding area, care must be taken to minimize environmental contamination and to maximize the effectiveness of cleaning (decontamination) activities. The design of such areas must include surfaces that are readily cleaned and decontaminated. Upholstered and carpeted surfaces should be avoided, as they are not readily cleaned. Several studies have shown floor contamination and the ineffectiveness of cleaning practices on both floors and surfaces.<sup>29,30,46</sup> Break rooms and refreshment areas for staff, patients, and others should be located away from areas of potential contamination to reduce unnecessary exposure to staff, visitors, and others.

Hazardous drugs may also be administered in nontraditional locations, such as the operating room, which present challenges to training and containment. Intracavitary administration of hazardous drugs (e.g., into the bladder, peritoneal cavity, or chest cavity) frequently requires equipment for which locking connections may not be readily available or even possible. All staff members who handle hazardous drugs should receive safety training that includes recognition of hazardous drugs and appropriate spill response. Hazardous drug spill kits, containment bags, and disposal containers must be available in all areas where hazardous drugs are handled. Techniques and ancillary devices that minimize the risk of open systems should be used when administering hazardous drugs through unusual routes or in nontraditional locations.

**Ventilation Controls.** Ventilation or engineering controls are devices designed to eliminate or reduce worker exposure to chemical, biological, radiological, ergonomic, and physical hazards. Ventilated cabinets are a type of ventilation or engineering control designed for the purpose of worker pro-

tection.<sup>4</sup> These devices minimize worker exposure by controlling the emission of airborne contaminants. Depending on the design, ventilated cabinets may also be used to provide the critical environment necessary to compound sterile preparations. When asepsis is not required, a Class I BSC or a containment isolator may be used to handle hazardous drugs. When sterile hazardous drugs are being compounded, a Class II or III BSC or an isolator intended for aseptic preparation and containment is required.<sup>4</sup> Recommendations for work practices specific to BSCs and isolators are discussed later in these guidelines.

**Class II BSCs.** In the early 1980s, the Class II BSC was determined to reduce the exposure of pharmacy compounding staff to hazardous preparations, as measured by the mutational response to the Ames test by urine of exposed subjects.<sup>58,59</sup> Studies in the 1990s, using analytical methods significantly more specific and sensitive than the Ames test, indicated that environmental and worker contamination occurs in workplace settings despite the use of controls recommended in published guidelines, including the use of Class II BSCs.<sup>29-35,37-41,60,61</sup> The exact cause of contamination has yet to be determined. Studies have shown that (1) there is contamination on the outside of vials received from manufacturers and distributors,<sup>30,54,55</sup> (2) work practices required to maximize the effectiveness of the Class II BSC are neglected or not taught,<sup>32,46</sup> and (3) the potential vaporization of hazardous drug solutions may reduce the effectiveness of the high-efficiency particulate air (HEPA) filter in providing containment.<sup>42-45</sup> Studies of surface contamination have discovered deposits of hazardous drugs on the floor in front of the Class II BSC, indicating that drug may have escaped through the open front of the BSC onto contaminated gloves or the final product or into the air.<sup>29-32</sup>

Workers must understand that the Class II BSC does not prevent the generation of contamination within the cabinet and that the effectiveness of such cabinets in containing hazardous drug contamination depends on operators' use of proper technique.

Some Class II BSCs recirculate airflow within the cabinet or exhaust contaminated air back into the work environment through HEPA filters.<sup>62</sup> The Class II BSC is designed with air plenums that are unreachable for surface decontamination; the plenum under the work tray collects room dirt and debris that mix with hazardous drug residue when the BSC is operational.<sup>1</sup> Drafts, supply-air louvers, and other laminar flow equipment placed near the BSC can interfere with the containment properties of the inflow air barrier, resulting in contamination of the work environment.<sup>63</sup> More information on the design and use of Class II BSCs is available from the NSF International (NSF)/American National Standards Institute (ANSI) standard 49-04.<sup>62</sup> Recommendations for use of Class II BSCs are listed in Appendix A.

**Alternatives to Class II BSCs.** Alternatives to the open-front Class II BSC include the Class III BSC, glove boxes, and isolators. By definition, a Class III BSC is a totally enclosed, ventilated cabinet of leak-tight construction.<sup>64</sup> Operations in the cabinet are conducted through fixed-glove access. The cabinet is maintained under negative air pressure. Supply air is drawn into the cabinet through HEPA filters. The exhaust air is treated by double HEPA filtration or by HEPA filtration and incineration. The Class III BSC is designed for use with highly toxic or infectious material. Because of the costs of

purchasing and operating a Class III BSC, it is seldom used for extemporaneous compounding of sterile products.

Less rigorous equipment with similar fixed-glove access include glove boxes and isolators. Although standardized definitions and criteria exist for glove boxes, these guidelines currently focus on applications in the nuclear industry and not on compounding hazardous drugs.<sup>65</sup> There are no standardized definitions or criteria for pharmaceutical compounding applications for this equipment and no performance standards determined by an independent organization to aid the purchaser in the selection process. NIOSH recommends that only ventilated engineering controls be used to compound hazardous drugs and that these controls be designed for containment.<sup>4</sup> NIOSH defines these controls and details their use and selection criteria as well as recommendations for airflow, exhaust, and maintenance. NIOSH further differentiates between ventilated engineering controls used for hazard containment that are intended for use with sterile products (aseptic containment) and those for use with nonsterile handling of hazardous drugs.<sup>4</sup>

An isolator may be considered a ventilated controlled environment that has fixed walls, floor, and ceiling. For aseptic use, supply air must be drawn through a high-efficiency (minimum HEPA) filter. Exhaust air must also be high-efficiency filtered and should be exhausted to the outside of the facility, not to the workroom. Workers access the isolator's work area, or main chamber, through gloves, sleeves, and air locks or pass-throughs. Currently available isolators have either unidirectional or turbulent airflow within the main chamber. For compounding sterile preparations, the filtered air and airflow must achieve an ISO class 5 (former FS-209E class 100) environment within the isolator.<sup>50,51,66,67</sup> Isolators for sterile compounding have become increasingly popular as a way to minimize the challenges of a traditional cleanroom and some of the disadvantages of the Class II BSC.<sup>50,68-70</sup> The totally enclosed design may reduce the escape of contamination during the compounding process. The isolator may be less sensitive to drafts and other laminar-airflow equipment, including positive-pressure environments. Issues unique to isolators include pressure changes when accessing the fixed-glove assembly, pressure changes in the main chamber when accessing the antechamber or pass-through, positive- versus negative-pressure isolators used to compound hazardous drugs, and ergonomic considerations associated with a fixed-glove assembly. Many isolators produce less heat and noise than Class II BSCs.<sup>68</sup> The Controlled Environment Testing Association has developed an applications guide for isolators in health care facilities.<sup>71</sup>

Isolators, like Class II BSCs, do not prevent the generation of contamination within the cabinet workspace, and their effectiveness in containing contamination depends on proper technique.<sup>72</sup> The potential for the spread of hazardous drug contamination from the pass-through and main chamber of the isolator to the workroom may be reduced by surface decontamination, but no wipe-down procedures have been studied. Surface decontamination may be more readily conducted in isolators than in Class II BSCs. (See *Decontamination, deactivation, and cleaning* for more information.)

Recirculating isolators depend on high-efficiency (HEPA or ultra-low penetrating air [ULPA]) filters. These filters may not sufficiently remove volatile hazardous drug contamination from the airflow. Isolators that discharge air into the workroom, even through high-efficiency filters,

present exposure concerns similar to those of unvented Class II BSCs if there is a possibility that the hazardous drugs handled in them may vaporize. Isolators used for compounding hazardous drugs should be at negative pressure or use a pressurized air lock to the surrounding areas to improve containment. Some isolators rely on a low-particulate environment rather than laminar-airflow technology to protect the sterility of the preparations. Recommendations for use of Class III BSCs and isolators are summarized in Appendix B.

*Closed-system drug-transfer devices.* Closed-system drug-transfer devices mechanically prevent the transfer of environmental contaminants into the system and the escape of drug or vapor out of the system.<sup>4</sup> ADD-Vantage and Duplex devices are closed-system drug-transfer devices currently available for injectable antibiotics. A similar system that may offer increased environmental protection for hazardous drugs is a proprietary, closed-system drug-transfer device known as PhaSeal. This multicomponent system uses a double membrane to enclose a specially cut injection cannula as it moves into a drug vial, Luer-Lok, or infusion-set connector.

Several studies have shown a reduction in environmental contamination with marker hazardous drugs during both compounding and administration when comparing standard techniques for handling hazardous drugs with the use of PhaSeal.<sup>73-78</sup> It should be noted, however, that PhaSeal components cannot be used to compound all hazardous drugs.

In 1984, Hoy and Stump<sup>79</sup> concluded that a commercial air-venting device reduced the release of drug aerosols during reconstitution of drugs packaged in vials. The testing was limited to visual analysis. The venting device does not lock onto the vial, which allows it to be transferred from one vial to another. This practice creates an opportunity for both environmental and product contamination. Many devices labeled as "chemo adjuncts" are currently available. Many feature a filtered, vented spike to facilitate reconstituting and removing hazardous drugs during the compounding process. However, none of these devices may be considered a closed-system drug-transfer device, and none has been formally studied with the results published in peer-reviewed journals. As other products become available, they should meet the definition of closed-system drug-transfer devices established by NIOSH<sup>4</sup> and should be required to demonstrate their effectiveness in independent studies. Closed-system drug-transfer devices (or any other ancillary devices) are not a substitute for using a ventilated cabinet.

*Personal Protective Equipment. Gloves.* Gloves are essential for handling hazardous drugs. Gloves must be worn at all times when handling drug packaging, cartons, and vials, including while performing inventory control procedures and when gathering hazardous drugs and supplies for compounding a batch or single dose. During compounding in a Class II BSC, gloves and gowns are required to prevent skin surfaces from coming into contact with these agents. Studies of gloves indicate that many latex and nonlatex materials are effective protection against penetration and permeation by most hazardous drugs.<sup>80-84</sup> Recent concerns about latex sensitivity have prompted testing of newer glove materials. Gloves made of nitrile or neoprene rubber and polyurethane have been successfully tested using a battery of antineoplastic drugs.<sup>82-84</sup> The American Society for Testing and Materials (ASTM) has developed testing standards for assessing the

resistance of medical gloves to permeation by chemotherapy drugs.<sup>85</sup> Gloves that meet this standard earn the designation of "chemotherapy gloves." Gloves selected for use with hazardous drugs should meet this ASTM standard.

Connor and Xiang<sup>86</sup> studied the effect of isopropyl alcohol on the permeability of latex and nitrile gloves exposed to antineoplastic agents. During the limited study period of 30 minutes, they found that the use of isopropyl alcohol during cleaning and decontaminating did not appear to affect the integrity of either material when challenged with six antineoplastic agents.

In most glove-testing systems, the glove material remains static, in contrast to the stressing and flexing that occur during actual use. In one study designed to examine glove permeability under static and flexed conditions, no significant difference in permeation was reported, except in thin latex examination gloves.<sup>87</sup> Another study, however, detected permeation of antineoplastic drugs through latex gloves during actual working conditions by using a cotton glove under the latex glove.<sup>88</sup> The breakthrough time for cyclophosphamide was only 10 minutes. The authors speculated that the cotton glove may have acted as a wick, drawing the hazardous drug through the outer glove. Nonetheless, under actual working conditions, double gloving and wearing gloves no longer than 30 minutes are prudent practices.

Permeability of gloves to hazardous drugs has been shown to be dependent on the drug, glove material and thickness, and exposure time. Powder-free gloves are preferred because powder particulates can contaminate the sterile processing area and absorb hazardous drug contaminants, which may increase the potential for dermal contact. Hands should be thoroughly washed before donning gloves and after removing them. Care must be taken when removing gloves in order to prevent the spreading of hazardous drug contaminants.

Several studies have indicated that contamination of the outside of gloves with hazardous drug is common after compounding and that this contamination may be spread to other surfaces during the compounding process.<sup>30-33,39</sup> Studies have also shown that hazardous drug contamination may lead to dermal absorption by workers not actively involved in the compounding and administration of hazardous drugs.<sup>30,88</sup> The use of two pairs of gloves is recommended when compounding these drugs. In an isolator, one additional pair of gloves must be worn within the fixed-glove assembly.<sup>88</sup>

Once compounding has been completed and the final preparation surface decontaminated, the outer glove should be removed and contained inside the BSC. The inner glove is worn to affix labels and place the preparation into a sealable containment bag for transport. This must be done within the BSC. In the isolator, the fixed gloves must be surface cleaned before wiping down the final preparation, placing the label onto the preparation, and placing it into the pass-through. The inner gloves should be worn to complete labeling and to place the final preparation into a transport bag in the pass-through. The inner gloves may then be removed and contained in a sealable bag within the pass-through. If the final check is conducted by a second staff member, fresh gloves must be donned before handling the completed preparation.

During batch compounding, gloves should be changed at least every 30 minutes. Gloves (at least the outer gloves) must be changed whenever it is necessary to exit and re-enter

the BSC. For aseptic protection of sterile preparations, the outer gloves must be sanitized with an appropriate disinfectant when reentering the BSC. Gloves must also be changed immediately if torn, punctured, or knowingly contaminated. When wearing two pairs of gloves in the BSC, one pair is worn under the gown cuff and the second pair placed over the cuff. When removing the gloves, the contaminated glove fingers must only touch the outer surface of the glove, never the inner surface. If the inner glove becomes contaminated, then both pairs of gloves must be changed. When removing any PPE, care must be taken to avoid introducing hazardous drug contamination into the environment. Both the inner and outer gloves should be considered contaminated, and glove surfaces must never touch the skin or any surface that may be touched by the unprotected skin of others. Gloves used to handle hazardous drugs should be placed in a sealable plastic bag for containment within the BSC or isolator pass-through before disposal as contaminated waste.

If an i.v. set is attached to the final preparation in the BSC or isolator, care must be taken to avoid contaminating the tubing with hazardous drug from the surface of the gloves, BSC, or isolator.

Class III BSCs and isolators are equipped with attached gloves or gauntlets. They should be considered contaminated once the BSC or isolator has been used for compounding hazardous drugs. For compounding sterile preparations, attached gloves or gauntlets must be routinely sanitized per the manufacturer's instructions to prevent microbial contamination. Hazardous drug contamination from the gloves or gauntlets may be transferred to the surfaces of all items within the cabinet. Glove and gauntlet surfaces must be cleaned after compounding is complete. All final preparations must be surface decontaminated by staff, wearing clean gloves to avoid spreading contamination.<sup>88</sup> Recommendations for use of gloves are summarized in Appendix C.

**Gowns.** Gowns or coveralls are worn during the compounding of sterile preparations to protect the preparation from the worker, to protect the worker from the preparation, or both. The selection of gowning materials depends on the goal of the process. Personal protective gowns are recommended during the handling of hazardous drug preparations to protect the worker from inadvertent exposure to extraneous drug particles on surfaces or generated during the compounding process.

Guidelines for the safe handling of hazardous drugs recommend the use of gowns for compounding in the BSC, administration, spill control, and waste management to protect the worker from contamination by fugitive drug generated during the handling process.<sup>1-4,89,90</sup> Early recommendations for barrier protective gowns required that they be disposable and made of a lint-free, low-permeability fabric with a closed front, long sleeves, and tight-fitting elastic or knit cuffs.<sup>1</sup> Washable garments (e.g., laboratory coats, scrubs, and cloth gowns) absorb fluids and provide no barrier against hazardous drug absorption and permeation. Studies into the effectiveness of disposable gowns in resisting permeation by hazardous drugs found variation in the protection provided by commercially available materials. In an evaluation of polypropylene-based gowns, Connor<sup>91</sup> found that polypropylene spun-bond nonwoven material alone and polypropylene-polyethylene copolymer spun-bond provided little protection against permeation by a battery of aqueous-

and nonaqueous-based hazardous drugs. Various constructions of polypropylene (e.g., spun-bond/melt-blown/spun-bond) result in materials that are completely impermeable or only slightly permeable to hazardous drugs. Connor<sup>91</sup> noted that these coated materials are similar in appearance to several other nonwoven materials but perform differently and that workers could expect to be protected from exposure for up to four hours when using the coated gowning materials. Harrison and Kloos<sup>92</sup> reported similar findings in a study of six disposable gowning materials and 15 hazardous drugs. Only gowns with polyethylene or vinyl coatings provided adequate splash protection and prevented drug permeation. In a subjective assessment of worker comfort, the more protective gowns were found to be warmer and thus less comfortable. These findings agree with an earlier study that found that the most protective gowning materials were the most uncomfortable to wear.<sup>93</sup> Resistance to the use of gowns, especially by nurses during administration of hazardous drugs, has been reported.<sup>94</sup> The lack of comfort could cause resistance to behavioral change.

Researchers have looked at gown contamination with fluorescent scans, high-performance liquid chromatography, and tandem mass spectrometry.<sup>39,95</sup> In one study, researchers scanned nurses and pharmacists wearing gowns during the compounding and administration of hazardous drugs.<sup>95</sup> Of a total of 18 contamination spots detected, 5 were present on the gowns of nurses after drug administration. No spots were discovered on the gowns of pharmacists after compounding. In contrast, researchers using a more sensitive assay placed pads in various body locations, both over and under the gowns used by the subjects during compounding and administration of cyclophosphamide and ifosfamide.<sup>39</sup> Workers wore short-sleeved nursing uniforms, disposable or cotton gowns, and vinyl or latex gloves. More contamination was found during compounding than administration. Contamination found on the pads placed on the arms of preparers is consistent with the design and typical work practices used in a Class II BSC, where the hands and arms are extended into the contaminated work area of the cabinet. Remarkably, one preparer had contamination on the back of the gown, possibly indicating touch contamination with the Class II BSC during removal of the final product. While early guidelines do not contain a maximum length of time that a gown should be worn, Connor's<sup>91</sup> work would support a two- to three-hour window for a coated gown. Contamination of gowns during glove changes must be a consideration. If the inner pair of gloves requires changing, a gown change should be considered. Gowns worn as barrier protection in the compounding of hazardous drugs must never be worn outside the immediate preparation area. Gowns worn during administration should be changed when leaving the patient care area and immediately if contaminated. Gowns should be removed carefully and properly disposed of as contaminated waste to avoid becoming a source of contamination to other staff and the environment.

Hazardous drug compounding in an enclosed environment, such as a Class III BSC or an isolator, may not require the operator to wear a gown. However, because the process of handling drug vials and final preparations, as well as accessing the isolator's pass-throughs, may present an opportunity for contamination, the donning of a gown is prudent. Coated gowns may not be necessary for this use if appropri-

ate gowning practices are established. Recommendations for use of gowns are summarized in Appendix D.

*Additional PPE.* Eye and face protection should be used whenever there is a possibility of exposure from splashing or uncontrolled aerosolization of hazardous drugs (e.g., when containing a spill or handling a damaged shipping carton). In these instances, a face shield, rather than safety glasses or goggles, is recommended because of the improved skin protection afforded by the shield.

Similar circumstances also warrant the use of a respirator. All workers who may use a respirator must be fit-tested and trained to use the appropriate respirator according to the OSHA Respiratory Protection Standard.<sup>56,57</sup> A respirator of correct size and appropriate to the aerosol size, physical state (i.e., particulate or vapor), and concentration of the airborne drug must be available at all times. Surgical masks do not provide respiratory protection. Shoe and hair coverings should be worn during the sterile compounding process to minimize particulate contamination of the critical work zone and the preparation.<sup>50</sup> With the potential for hazardous drug contamination on the floor in the compounding and administration areas, shoe coverings are recommended as contamination-control mechanisms. Shoe coverings must be removed with gloved hands when leaving the compounding area. Gloves should be worn and care must be taken when removing hair or shoe coverings to prevent contamination from spreading to clean areas. Hair and shoe coverings used in the hazardous drug handling areas must be contained, along with used gloves, and discarded as contaminated waste.

*Work Practices. Compounding sterile hazardous drugs.* Work practices for the compounding of sterile hazardous drugs differ somewhat with the use of a Class II BSC, a Class III BSC, or an isolator. Good organizational skills are essential to minimize contamination and maximize productivity. All activities not requiring a critical environment (e.g., checking labels, doing calculations) should be completed before accessing the BSC or isolator. All items needed for compounding must be gathered before beginning work. This practice should eliminate the need to exit the BSC or isolator once compounding has begun. Two pairs of gloves should be worn to gather hazardous drug vials and supplies. These gloves should be carefully removed and discarded. Fresh gloves must be donned and appropriately sanitized before aseptic manipulation.

Only supplies and drugs essential to compounding the dose or batch should be placed in the work area of the BSC or main chamber of the isolator. BSCs and isolators should not be overcrowded to avoid unnecessary hazardous drug contamination. Luer-Lok syringes and connections must be used whenever possible for manipulating hazardous drugs, as they are less likely to separate during compounding.

Spiking an i.v. set into a solution containing hazardous drugs or priming an i.v. set with hazardous drug solution in an uncontrolled environment must be avoided. One recommendation is to attach and prime the appropriate i.v. set to the final container in the BSC or isolator before adding the hazardous drug. Closed-system drug-transfer devices should achieve a dry connection between the administration set and the hazardous drug's final container. This connection allows the container to be spiked with a secondary i.v. set and the set to be primed by backflow from a primary nonhazardous solution. This process may be done outside the BSC or isolator, reducing the potential for surface contamination of the

i.v. set during the compounding process. A new i.v. set must be used with each dose of hazardous drug. Once attached, the i.v. set must never be removed from a hazardous drug dose, thereby preventing the residual fluid in the bag, bottle, or tubing from leaking and contaminating personnel and the environment.

Transport bags must never be placed in the BSC or in the isolator work chamber during compounding to avoid inadvertent contamination of the outer surface of the bag. Final preparations must be surface decontaminated after compounding is complete. In either the BSC or isolator, clean inner gloves must be worn when labeling and placing the final preparation into the transport bag. Handling final preparations and transport bags with gloves contaminated with hazardous drugs will result in the transfer of the contamination to other workers. Don fresh gloves whenever there is a doubt as to the cleanliness of the inner or outer gloves.

*Working in BSCs or isolators.* With or without ancillary devices, none of the available ventilation or engineering controls can provide 100% protection for the worker. Workers must recognize the limitations of the equipment and address them through appropriate work practices.<sup>1</sup> The effectiveness of Class II BSCs and isolators in containing contamination depends on proper technique.<sup>72</sup> Hazardous drug contamination from the work area of the isolator may be brought into the workroom environment through the pass-throughs or air locks and on the surfaces of items removed from the isolators (e.g., the final preparation). Surface decontamination of the preparation before removal from the isolator's main chamber should reduce the hazardous drug contamination that could be transferred to the workroom, but no wipe-down procedures have been studied. Surface decontamination may be accomplished using alcohol, sterile water, peroxide, or sodium hypochlorite solutions, provided the packaging is not permeable to the solution and the labels remain legible and intact. Recommendations for working in BSCs and isolators are summarized in Appendix E.

*BSCs.* Class II BSCs use vertical-flow, HEPA-filtered air (ISO class 5) as their controlled aseptic environment. Before beginning an operation in a Class II BSC, personnel should wash their hands, don an inner pair of appropriate gloves, and then don a coated gown followed by a second pair of gloves. The work surface should be cleaned of surface contamination with detergent, sodium hypochlorite, and neutralizer or disinfected with alcohol, depending on when it was last cleaned. For the Class II BSC, the front shield must be lowered to the proper level to protect the face and eyes. The operator should be seated so that his or her shoulders are at the level of the bottom of the front shield. All drugs and supplies needed to aseptically compound a dose or batch should be gathered and sanitized with 70% alcohol or appropriate disinfectant. Avoid exiting and reentering the work area. Being careful not to place any sterile objects below them, i.v. bags and bottles may be hung from the bar. All items must be placed well within the Class II BSC, away from the unfiltered air at the front barrier. By design, the intended work zone within the Class II BSC is the area between the front and rear air grilles. The containment characteristics of the Class II BSC are dependent on the airflow through both the front and back grilles; these grilles should never be obstructed. Due to the design of the Class II BSC, the quality of HEPA-filtered air is lowest at the sides of the

work zone, so manipulations should be performed at least six inches away from each sidewall in the horizontal plane. A small waste-sharps container may be placed along the sidewall toward the back of the BSC. One study has suggested that a plastic-backed absorbent preparation pad in a Class II BSC may interfere with airflow,<sup>99</sup> but another study determined that use of a flat firm pad that did not block the grilles of the cabinet had no effect on airflow.<sup>96</sup> The use of a large pad that might block the front or rear grilles must be avoided. In addition, because a pad may absorb small spills, it may become a source of hazardous drug contamination for anything placed upon it. Preparation pads are not readily decontaminated and must be replaced and discarded after preparation of each batch and frequently during extended batch compounding. More information on the design and use of Class II BSCs is available from the NSF/ANSI standard 49-04.<sup>62</sup>

*Isolators.* For work in an isolator, all drugs and supplies needed to aseptically compound a dose or batch should be gathered and sanitized with 70% alcohol or appropriate disinfectant and readied for placement in the pass-through. A technique described in the literature involves the use of a tray that will fit into the pass-through.<sup>97</sup> A large primary sealable bag is placed over the tray. Labels and a second sealable (transport) bag, which is used to contain the final preparation, are placed into the primary sealable bag on the tray surface. Vials, syringes, needles, and other disposables are placed on top of the sealed bag. The enclosed tray is then taken into the main chamber of the isolator, where the drug and supplies are used to compound the dose. The contaminated materials, including the primary sealable bag, are removed using the closed trash system of the isolator, if so equipped, or sealed into a second bag and removed via the pass-through for disposal as contaminated waste. The dose is then labeled and placed into the second sealable bag for transport.

This technique does not address contamination on the isolator gloves or gauntlets. Additional work practices may include cleaning off the gloves or gauntlets and final preparation after initial compounding and before handling the label and second sealable bag. Care must be taken when transferring products out of the pass-through and disposing of waste through the pass-through or trash chute to avoid accidental contamination.

*Aseptic technique.* Stringent aseptic technique, described by Wilson and Solimando<sup>98</sup> in 1981, remains the foundation of any procedure involving the use of needles and syringes in manipulating sterile dosage forms. This technique, when performed in conjunction with negative pressure technique, minimizes the escape of drug from vials and ampuls. Needleless devices have been developed to reduce the risk of blood-borne pathogen exposure through needle sticks. None of these devices has been tested for reduction of hazardous drug contamination. The appropriateness of these devices in the safe handling of hazardous drugs has not been determined.

In reconstituting hazardous drugs in vials, it is critical to avoid pressurizing the contents of the vial. Pressurization may cause the drug to spray out around the needle or through a needle hole or a loose seal, aerosolizing the drug into the work zone. Pressurization can be avoided by creating a slight negative pressure in the vial. Too much negative pressure, however, can cause leakage from the needle when it is with-

drawn from the vial. The safe handling of hazardous drug solutions in vials or ampuls requires the use of a syringe that is no more than three-fourths full when filled with the solution, which minimizes the risk of the plunger separating from the syringe barrel. Once the diluent is drawn up, the needle is inserted into the vial and the plunger is pulled back (to create a slight negative pressure inside the vial), so that air is drawn into the syringe. Small amounts of diluent should be transferred slowly as equal volumes of air are removed. The needle should be kept in the vial, and the contents should be swirled carefully until dissolved. With the vial inverted, the proper amount of drug solution should be gradually withdrawn while equal volumes of air are exchanged for solution. The exact volume needed must be measured while the needle is in the vial, and any excess drug should remain in the vial. With the vial in the upright position, the plunger should be withdrawn past the original starting point to again induce a slight negative pressure before removing the needle. The needle hub should be clear before the needle is removed.

If a hazardous drug is transferred to an i.v. bag, care must be taken to puncture only the septum of the injection port and avoid puncturing the sides of the port or bag. After the drug solution is injected into the i.v. bag, the i.v. port, container, and set (if attached by pharmacy in the BSC or isolator) should be surface decontaminated. The final preparation should be labeled, including an auxiliary warning, and the injection port covered with a protective shield. The final container should be placed, using clean gloves, into a sealable bag to contain any leakage.<sup>1</sup>

To withdraw hazardous drugs from an ampul, the neck or top portion should be gently tapped.<sup>98</sup> After the neck is wiped with alcohol, a 5- $\mu$ m filter needle or straw should be attached to a syringe that is large enough that it will be not more than three-fourths full when holding the drug. The fluid should then be drawn through the filter needle or straw and cleared from the needle and hub. After this, the needle or straw is exchanged for a needle of similar gauge and length; any air and excess drug should be ejected into a sterile vial (leaving the desired volume in the syringe); aerosolization should be avoided. The drug may then be transferred to an i.v. bag or bottle. If the dose is to be dispensed in the syringe, the plunger should be drawn back to clear fluid from the needle and hub. The needle should be replaced with a locking cap, and the syringe should be surface decontaminated and labeled.

*Training and demonstration of competence.* All staff who will be compounding hazardous drugs must be trained in the stringent aseptic and negative-pressure techniques necessary for working with sterile hazardous drugs. Once trained, staff must demonstrate competence by an objective method, and competency must be reassessed on a regular basis.<sup>99</sup>

*Preparation and handling of noninjectable hazardous drug dosage forms.* Although noninjectable dosage forms of hazardous drugs contain varying proportions of drug to nondrug (nonhazardous) components, there is the potential for personnel exposure to and environmental contamination with the hazardous components if hazardous drugs are handled (e.g., packaged) by pharmacy staff. Although most hazardous drugs are not available in liquid formulations, such formulations are often prescribed for small children and adults with feeding tubes. Recipes for extemporane-

ously compounded oral liquids may start with the parenteral form, or they may require that tablets be crushed or capsules opened. Tablet trituration has been shown to cause fine dust formation and local environmental contamination.<sup>100</sup> Procedures for the preparation and the use of equipment (e.g., Class I BSCs or bench-top hoods with HEPA filters) must be developed to avoid the release of aerosolized powder or liquid into the environment during manipulation of hazardous drugs. Recommendations for preparation and handling of noninjectable hazardous drug dosage forms are summarized in Appendix F.

*Decontamination, deactivation, and cleaning.* Decontamination may be defined as cleaning or deactivating. Deactivating a hazardous substance is preferred, but no single process has been found to deactivate all currently available hazardous drugs. The use of alcohol for disinfecting the BSC or isolator will not deactivate any hazardous drugs and may result in the spread of contamination rather than any actual cleaning.<sup>30,47</sup>

Decontamination of BSCs and isolators should be conducted per manufacturer recommendations. The MSDSs for many hazardous drugs recommend sodium hypochlorite solution as an appropriate deactivating agent.<sup>101</sup> Researchers have shown that strong oxidizing agents, such as sodium hypochlorite, are effective deactivators of many hazardous drugs.<sup>102,103</sup> There is currently one commercially available product, SurfaceSafe (SuperGen, Dublin, CA), that provides a system for decontamination and deactivation using sodium hypochlorite, detergent, and thiosulfate neutralizer. A ventilated cabinet that runs continuously should be cleaned before the day's operations begin and at regular intervals or when the day's work is completed. For a 24-hour service, the cabinet should be cleaned two or three times daily. Cabinets used for aseptic compounding must be disinfected at the beginning of the workday, at the beginning of each subsequent shift (if compounding takes place over an extended period of time), and routinely during compounding.

Appropriate preparation of materials used in compounding before introduction into the Class II BSC or the pass-through of a Class III BSC or isolator, including spraying or wiping with 70% alcohol or appropriate disinfectant, is also necessary for aseptic compounding.

The Class II BSC has air plenums that handle contaminated air. These plenums are not designed to allow surface decontamination, and many of the contaminated surfaces (plenums) cannot be reached for surface cleaning. The area under the work tray should be cleaned at least monthly to reduce the contamination level in the Class II BSC (and in isolators, where appropriate).

Surface decontamination may be accomplished by the transfer of hazardous drug contamination from the surface of a nondisposable item to disposable ones (e.g., wipes, gauze, towels). Although the outer surface of vials containing hazardous drugs has been shown to be contaminated with hazardous drugs,<sup>30,54,55</sup> and hazardous drug contamination has been found on the outside of final preparations,<sup>30</sup> no wipe-down procedures have been studied. The amount of hazardous drug contamination placed into the BSC or isolator may be reduced by surface decontamination (i.e., wiping down) of hazardous drug vials. While no wipe-down procedures have been studied, the use of gauze moistened with alcohol, sterile water, peroxide, or sodium hypochlorite solutions

may be effective. The disposable item, once contaminated, must be contained and discarded as contaminated waste.

*Administration of hazardous drugs.* Policies and procedures governing the administration of hazardous drugs must be jointly developed by nursing and pharmacy for the mutual safety of health care workers. These policies should supplement policies designed to protect patient safety during administration of all drugs. All policies affecting multiple departments must be developed with input from managers and workers from the affected areas. Extensive nursing guidelines for the safe and appropriate administration of hazardous drugs have been developed by the Oncology Nursing Society<sup>90,104</sup> and OSHA.<sup>2,3</sup> Recommendations for reducing exposure to hazardous drugs during administration in all practice settings are listed in Appendix G.

*Spill management.* Policies and procedures must be developed to attempt to prevent spills and to govern cleanup of hazardous drug spills. Written procedures must specify who is responsible for spill management and must address the size and scope of the spill. Spills must be contained and cleaned up immediately by trained workers.

Spill kits containing all of the materials needed to clean up spills of hazardous drugs should be assembled or purchased (Appendix H). These kits should be readily available in all areas where hazardous drugs are routinely handled. A spill kit should accompany delivery of injectable hazardous drugs to patient care areas even though they are transported in a sealable plastic bag or container. If hazardous drugs are being prepared or administered in a nonroutine area (e.g., home setting, unusual patient care area), a spill kit and respirator must be obtained by the drug handler. Signs should be available to warn of restricted access to the spill area.

Only trained workers with appropriate PPE and respirators should attempt to manage a hazardous drug spill. All workers who may be required to clean up a spill of hazardous drugs must receive proper training in spill management and in the use of PPE and NIOSH-certified respirators.

The circumstances and handling of spills should be documented. Staff and nonemployees exposed to a hazardous drug spill should also complete an incident report or exposure form and report to the designated emergency service for initial evaluation.

All spill materials must be disposed of as hazardous waste.<sup>105</sup> Recommendations for spill cleanup procedure are summarized in Appendix I.

*Worker contamination.* Procedures must be in place to address worker contamination, and protocols for medical attention must be developed before the occurrence of any such incident. Emergency kits containing isotonic eyewash supplies (or emergency eyewashes, if available) and soap must be immediately available in areas where hazardous drugs are handled. Workers who are contaminated during the spill or spill cleanup or who have direct skin or eye contact with hazardous drugs require immediate treatment. OSHA-recommended steps for treatment are outlined in Appendix J.

*Hazardous Waste Containment and Disposal.* In 1976, the Resource Conservation and Recovery Act (RCRA) was enacted to provide a mechanism for tracking hazardous waste from its generation to disposal.<sup>106</sup> Regulations promulgated under RCRA are enforced by the Environmental Protection Agency and apply to pharmaceuticals and chemicals discarded by pharmacies, hospitals, clinics, and other commer-

cial entities. The RCRA outlines four "characteristics" of hazardous waste<sup>107</sup> and contains lists of agents that are to be considered hazardous waste when they are discarded.<sup>108</sup> Any discarded drug that is on one of the lists (a "listed" waste) or meets one of the criteria (a "characteristic" waste) is considered hazardous waste. The listed drugs include epinephrine, nicotine, and physostigmine, as well as nine chemotherapy drugs: arsenic trioxide, chlorambucil, cyclophosphamide, daunomycin, diethylstilbestrol, melphalan, mitomycin C, streptozocin, and uracil mustard. They require handling, containment, and disposal as RCRA hazardous waste.

The RCRA allows for the exemption of "empty containers" from hazardous waste regulations. Empty containers are defined as those that have held U-listed or characteristic wastes and from which all wastes have been removed that can be removed using the practices commonly employed to remove materials from that type of container and no more than 3% by weight of the total capacity of the container remains in the container.<sup>109</sup> Disposal guidelines developed by the National Institutes of Health (NIH) and published in 1984 coined the term "trace-contaminated" waste using the 3% rule.<sup>110</sup> Note that a container that has held an acute hazardous waste listed in §§261.31, 261.32, or 261.33(e), such as arsenic trioxide, is not considered empty by the 3% rule,<sup>111</sup> and that spill residues from cleanup of hazardous agents are considered hazardous waste.<sup>105</sup>

In addition, many states are authorized to implement their own hazardous waste programs, and requirements under these programs may be more stringent than those of the EPA. State and local regulations must be considered when establishing a hazardous waste policy for a specific facility.

General categories of hazardous waste found in health care settings would include trace-contaminated hazardous waste, bulk hazardous waste, hazardous drugs not listed as hazardous waste, and hazardous waste and mixed infectious-hazardous waste.

*Trace-contaminated hazardous drug waste.* By the NIH definition of trace chemotherapy waste,<sup>110</sup> "RCRA-empty" containers, needles, syringes, trace-contaminated gowns, gloves, pads, and empty i.v. sets may be collected and incinerated at a regulated medical waste incinerator. Sharps used in the preparation of hazardous drugs should not be placed in red sharps containers or needle boxes, since these are most frequently disinfected by autoclaving or microwaving, not by incineration, and pose a risk of aerosolization to waste-handling employees.

*Bulk hazardous drug waste.* While not official, the term *bulk hazardous drug waste* has been used to differentiate containers that have held either (1) RCRA-listed or characteristic hazardous waste or (2) any hazardous drugs that are not RCRA empty or any materials from hazardous drug spill cleanups. These wastes should be managed as hazardous waste.

*Hazardous drugs not listed as hazardous waste.* The federal RCRA regulations have not kept up with drug development, as there are over 100 hazardous drugs that are not listed as hazardous waste, including hormonal agents. In some states, such as Minnesota, these must be managed as hazardous waste. In other states, organizations should manage these drugs as hazardous waste as a best-management practice until federal regulations can be updated.

*Hazardous waste and mixed infectious-hazardous waste.* Most hazardous waste vendors are not permitted to

manage regulated medical waste or infectious waste; therefore, they cannot accept used needles and items contaminated with squeezable, flakable, or drippable blood. Organizations should check carefully with their hazardous waste vendors to ensure acceptance of all possible hazardous waste, including mixed infectious waste, if needed. Once hazardous waste has been identified, it must be collected and stored according to specific EPA and Department of Transportation requirements.<sup>112</sup> Properly labeled, leakproof, and spill-proof containers of nonreactive plastic are required for areas where hazardous waste is generated. Hazardous drug waste may be initially contained in thick, sealable plastic bags before being placed in approved satellite accumulation containers. Glass fragments should be contained in small, puncture-resistant containers to be placed into larger containers approved for temporary storage.

Waste contaminated with blood or other body fluids must not be mixed with hazardous waste. Transport of waste containers from satellite accumulation to storage sites must be done by individuals who have completed OSHA-mandated hazardous waste awareness training.<sup>113,114</sup> Hazardous waste must be properly manifested and transported by a federally permitted hazardous waste transporter to a federally permitted hazardous waste storage, treatment, or disposal facility.<sup>115</sup> A licensed contractor may be hired to manage the hazardous waste program. The waste generator, however, may be held liable for mismanagement of hazardous waste. Investigation of a contractor, including verification of possession and type of license, should be completed and documented before a contractor is engaged. More information on hazardous waste disposal is available at [www.hercenter.org](http://www.hercenter.org).

**Alternative Duty and Medical Surveillance.** A comprehensive safety program for controlling workplace exposure to hazardous drugs must include engineering controls, training, work practices, and PPE. Such safety programs must be able to identify potentially exposed workers and those who might be at higher risk of adverse health effects due to this exposure. Because reproductive risks have been associated with exposure to hazardous drugs, alternative duty should be offered to individuals who are pregnant, breast-feeding, or attempting to conceive or father a child. Employees' physicians should be involved in making these determinations.

All workers who handle hazardous drugs should be routinely monitored in a medical surveillance program.<sup>2-4,90,104</sup> Medical surveillance involves the collection and interpretation of data for the purpose of detecting changes in the health status of working populations. Medical surveillance programs involve assessment and documentation of symptom complaints, physical findings, and laboratory values (such as a blood count) to determine whether there is a deviation from the expected norms. Descriptions of medical surveillance programs for hazardous drug handlers are presented in the literature.<sup>90,104</sup> NIOSH encourages employees who handle hazardous drugs to participate in medical surveillance programs that are provided in the workplace.<sup>4</sup> Limited resources may preclude the implementation of a comprehensive medical surveillance program for health care workers who are exposed to hazardous drugs. In the absence of an institutional medical surveillance program, NIOSH encourages workers handling hazardous drugs to inform their personal health

care providers of their occupation and possible hazardous drug exposure when obtaining routine medical care.<sup>4</sup>

## Conclusion

These guidelines represent the recommendations of many groups and individuals who have worked tirelessly over decades to reduce the potential of harmful effects on health care workers exposed to hazardous drugs. No set of guidelines on this topic, however comprehensive, can address all the needs of every health care facility. Health care professionals are encouraged to rely on their professional judgment, experience, and common sense in applying these recommendations to their unique circumstances and to take into account evolving federal, state, and local regulations, as well as the requirements of appropriate accrediting institutions.

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### Appendix A—Recommendations for Use of Class II BSCs

1. The use of a Class II BSC must be accompanied by a stringent program of work practices, including training, demonstrated competence, contamination reduction, and decontamination.
2. Only a Class II BSC with outside exhaust should be used for compounding hazardous drugs; type B2 total exhaust is preferred. Total exhaust is required if the hazardous drug is known to be volatile.<sup>4</sup>
3. Without special design considerations, Class II BSCs are not recommended in traditional, positive-pressure cleanrooms, where contamination from hazardous drugs may result in airborne contamination that may spread from the open front to surrounding areas.
4. Consider using closed-system drug-transfer devices while compounding hazardous drugs in a Class II BSC; evidence documents a decrease in drug contaminants inside a Class II BSC when such devices are used.<sup>4</sup>
5. Reduce the hazardous drug contamination burden in the Class II BSC by wiping down hazardous drug vials before placing them in the BSC.

### Appendix B—Recommendations for Use of Class III BSCs and Isolators

1. Only a ventilated cabinet appendix to protect workers and adjacent personnel from exposure and to provide an aseptic environment may be used to compound sterile hazardous drugs.
2. Only ventilated cabinets that are designed to contain aerosolized drug product within the cabinet should be used to compound hazardous drugs.
3. The use of a Class III BSC or isolator must be accompanied by a stringent program of work practices, including operator training and demonstrated competence, contamination reduction, and decontamination.
4. Decontamination of the Class III BSC or isolator must be done in a way that contains any hazardous drug surface contamination during the cleaning process.
5. Appropriate decontamination within the cabinet must be completed before the cabinet is accessed via pass-throughs or removable front panels.
6. Gloves or gauntlets must not be replaced before completion of appropriate decontamination within the cabinet.
7. Surface decontamination of final preparations must be done before labeling and placing into the pass-through.
8. Final preparations must be placed into a transport bag while in the pass-through for removal from the cabinet.

### Appendix C—Recommendations for Use of Gloves

1. Wear double gloves for all activities involving hazardous drugs. Double gloves must be worn during any handling of hazardous drug shipping cartons or drug vials, compounding and administration of hazardous

- drugs, handling of hazardous drug waste or waste from patients recently treated with hazardous drugs, and cleanup of hazardous drug spills.
2. Select powder-free, high-quality gloves made of latex, nitrile, polyurethane, neoprene, or other materials that meet the ASTM standard for chemotherapy gloves.
3. Inspect gloves for visible defects.
4. Sanitize gloves with 70% alcohol or other appropriate disinfectant before performing any aseptic compounding activity.
5. Change gloves every 30 minutes during compounding or immediately when damaged or contaminated.
6. Remove outer gloves after wiping down final preparation but before labeling or removing the preparation from the BSC.
7. Outer gloves must be placed in a containment bag while in the BSC.
8. In an isolator, a second glove must be worn inside the fixed-glove assembly.
9. In an isolator, fixed gloves or appendix must be surface cleaned after compounding is completed to avoid spreading hazardous drug contamination to other surfaces.
10. Clean gloves (e.g., the clean inner gloves) should be used to surface decontaminate the final preparation, place the label onto the final preparation, and place it into the pass-through.
11. Don fresh gloves to complete the final check, place preparation into a clean transport bag, and remove the bag from the pass-through.
12. Wash hands before donning and after removing gloves.
13. Remove gloves with care to avoid contamination. Specific procedures for removal must be established and followed.
14. Gloves should be removed and contained inside the Class II BSC or isolator.
15. Change gloves after administering a dose of hazardous drugs or when leaving the immediate administration area.
16. Dispose of contaminated gloves as contaminated waste.

### Appendix D—Recommendations for Use of Gowns

1. Gowns should be worn during compounding, during administration, when handling waste from patients recently treated with hazardous drugs, and when cleaning up spills of hazardous drugs.
2. Select disposable gowns of material tested to be protective against the hazardous drugs to be used.
3. Coated gowns must be worn no longer than three hours during compounding and changed immediately when damaged or contaminated.
4. Remove gowns with care to avoid spreading contamination. Specific procedures for removal must be established and followed.
5. Dispose of gowns immediately upon removal.
6. Contain and dispose of contaminated gowns as contaminated waste.
7. Wash hands after removing and disposing of gowns.

### Appendix E—Recommendations for Working in BSCs and Isolators

1. The use of a Class II or III BSC or isolator must be accompanied by a stringent program of work practices, including operator training and demonstrated competence, contamination reduction, and decontamination.
2. Do not place unnecessary items in the work area of the cabinet or isolator where hazardous drug contamination from compounding may settle on them.
3. Do not overcrowd the BSC or isolator.
4. Gather all needed supplies before beginning compounding. Avoid exiting and reentering the work area of the BSC or isolator.
5. Appropriate handling of the preparation in the BSC or pass-through of the isolator, including spraying or wiping with 70% alcohol or another appropriate disinfectant, is necessary for aseptic compounding.
6. Reduce the hazardous drug contamination burden in the BSC or isolator by wiping down hazardous drug vials before placing them in the BSC or isolator.
7. Transport bags must never be placed in the BSC or the isolator work chamber during compounding to avoid inadvertent contamination of the outside surface of the bag.
8. Final preparations should be surface decontaminated within the BSC or isolator and placed into the transport bags in the BSC or in the isolator pass-through, taking care not to contaminate the outside of the transport bag.
9. Decontaminate the work surface of the BSC or isolator before and after compounding per the manufacturer's recommendations or with detergent, sodium hypochlorite solution, and neutralizer.
10. Decontaminate all surfaces of the BSC or isolator at the end of the batch, day, or shift, as appropriate to the workflow. Typically, a BSC or isolator in use 24 hours a day would require decontamination two or three times daily. Disinfect the BSC or isolator before compounding a dose or batch of sterile hazardous drugs.
11. Wipe down the outside of the Class II BSC front opening and the floor in front of the BSC with detergent, sodium hypochlorite solution, and neutralizer at least daily.
12. Seal and then decontaminate surfaces of waste and sharps containers before removing from the BSC or isolator.
13. Decontamination is required after any spill in the BSC or isolator during compounding.
14. Seal all contaminated materials (e.g., gauze, wipes, towels, wash or rinse water) in bags or plastic containers and discard as contaminated waste.
15. Decontamination of the Class III BSC or isolator must be done in a way that contains any hazardous drug surface contamination during the cleaning process.
16. Appropriate decontamination within the cabinet must be completed before the cabinet is accessed via the pass-throughs or removable front panels.
17. Gloves or gauntlets must not be replaced before completion of appropriate decontamination within the cabinet.

18. Surface decontamination of final preparations must be done before labeling and placing into the pass-through.
19. Final preparations must be placed into a transport bag while in the pass-through for removal from the cabinet.

### Appendix F—Recommendations for Compounding and Handling Noninjectable Hazardous Drug Dosage Forms

1. Hazardous drugs should be labeled or otherwise identified as such to prevent improper handling.
2. Tablet and capsule forms of hazardous drugs should not be placed in automated counting machines, which subject them to stress and may introduce powdered contaminants into the work area.
3. During routine handling of noninjectable hazardous drugs and contaminated equipment, workers should wear two pairs of gloves that meet the ASTM standard for chemotherapy gloves.<sup>85</sup>
4. Counting and pouring of hazardous drugs should be done carefully, and clean equipment should be dedicated for use with these drugs.
5. Contaminated equipment should be cleaned initially with gauze saturated with sterile water; further cleaned with detergent, sodium hypochlorite solution, and neutralizer; and then rinsed. The gauze and rinse should be contained and disposed of as contaminated waste.
6. Crushing tablets or opening capsules should be avoided; liquid formulations should be used whenever possible.
7. During the compounding of hazardous drugs (e.g., crushing, dissolving, or preparing a solution or an ointment), workers should wear nonpermeable gowns and double gloves. Compounding should take place in a ventilated cabinet.
8. Compounding nonsterile forms of hazardous drugs in equipment designated for sterile products must be undertaken with care. Appropriate containment, deactivation, and disinfection techniques must be utilized.
9. Hazardous drugs should be dispensed in the final dose and form whenever possible. Unit-of-use containers for oral liquids have not been tested for containment properties. Most exhibit some spillage during preparation or use. Caution must be exercised when using these devices.
10. Bulk containers of liquid hazardous drugs, as well as specially packaged commercial hazardous drugs (e.g., Neoral [manufactured by Novartis]), must be handled carefully to avoid spills. These containers should be dispensed and maintained in sealable plastic bags to contain any inadvertent contamination.
11. Disposal of unused or unusable noninjectable dosage forms of hazardous drugs should be performed in the same manner as for hazardous injectable dosage forms and waste.

## Appendix G—Recommendations for Reducing Exposure to Hazardous Drugs During Administration in All Practice Settings<sup>104</sup>

### *Intravenous administration*

1. The use of gloves, gown, and face shield (as needed for splashing) is required.
2. Gather all necessary equipment and supplies, including PPE.
3. Use needleless systems whenever possible.
4. Use Luer-Lok fittings for all needleless systems, syringes, needles, infusion tubing, and pumps.
5. Needleless systems may result in droplets leaking at connection points; use gauze pads to catch leaks.
6. Designate a workplace for handling hazardous drugs.
7. Have a spill kit and hazardous drug waste container readily available.
8. Procedure for gowning and gloving: Wash hands, don first pair of gloves, don gown and face shield, and then don second pair of gloves. Gloves should extend beyond the elastic or knit cuff of the gown. Double-gloving requires one glove to be worn under the cuff of the gown and the second glove over the cuff.
9. Always work below eye level.
10. Visually examine hazardous drug dose while it is still contained in transport bag.
11. If hazardous drug dose appears intact, remove it from the transport bag.
12. Place a plastic-backed absorbent pad under the administration area to absorb leaks and prevent drug contact with the patient's skin.
13. If priming occurs at the administration site, prime i.v. tubing with an i.v. solution that does not contain hazardous drugs or by the backflow method.
14. Place a gauze pad under the connection at injection ports during administration to catch leaks.
15. Use the transport bag as a containment bag for materials contaminated with hazardous drugs, drug containers, and sets.
16. Discard hazardous drug containers with the administration sets attached; do not remove the set.
17. Wash surfaces that come into contact with hazardous drugs with detergent, sodium hypochlorite solution, and neutralizer, if appropriate.
18. Wearing gloves, contain and dispose of materials contaminated with hazardous drugs and remaining PPE as contaminated waste.
19. Hazardous drug waste container must be sufficiently large to hold all discarded material, including PPE.
20. Do not push or force materials contaminated with hazardous drugs into the hazardous drug waste container.
21. Carefully remove, contain, and discard gloves. Wash hands thoroughly after removing gloves.

### *Intramuscular or subcutaneous administration*

1. The use of double gloves is required.
2. Gather all necessary equipment and supplies, including PPE.
3. Use Luer-Lok safety needles or retracting needles or shields.

4. Syringes should have Luer-Lok connections and be less than three-fourths full.
5. Designate a workplace for handling hazardous drugs.
6. Have a spill kit and hazardous drug waste container readily available.
7. Procedure for gloving: Wash hands; don double gloves.
8. Always work below eye level.
9. Visually examine hazardous drug dose while still contained in transport bag.
10. If hazardous drug dose appears intact, remove it from the transport bag.
11. Remove the syringe cap and connect appropriate safety needle.
12. Do not expel air from syringe or prime the safety needle.
13. After administration, discard hazardous drug syringes (with the safety needle attached) directly into a hazardous drug waste container.
14. Wearing gloves, contain and dispose of materials contaminated with hazardous drugs.
15. Do not push or force materials contaminated with hazardous drugs into the hazardous drug waste container.
16. Carefully remove, contain, and discard gloves.
17. Wash hands thoroughly after removing gloves.

### *Oral administration*

1. Double gloves are required, as is a face shield if there is a potential for spraying, aerosolization, or splashing.
2. Workers should be aware that tablets or capsules may be coated with a dust of residual hazardous drug that could be inhaled, absorbed through the skin, ingested, or spread to other locations and that liquid formulations may be aerosolized or spilled.
3. No crushing or compounding of oral hazardous drugs may be done in an unprotected environment.
4. Gather all necessary equipment and supplies, including PPE.
5. Designate a workplace for handling hazardous drugs.
6. Have a spill kit and hazardous drug waste container readily available.
7. Procedure for gloving: Wash hands and don double gloves.
8. Always work below eye level.
9. Visually examine hazardous drug dose while it is still contained in transport bag.
10. If hazardous drug dose appears intact, remove it from the transport bag.
11. Place a plastic-backed absorbent pad on the work area, if necessary, to contain any spills.
12. After administration, wearing double gloves, contain and dispose of materials contaminated with hazardous drugs into the hazardous drug waste container.
13. Do not push or force materials contaminated with hazardous drugs into the hazardous drug waste container.
14. Carefully remove, contain, and discard gloves.
15. Wash hands thoroughly after removing gloves.

### Appendix H—Recommended Contents of Hazardous Drug Spill Kit

1. Sufficient supplies to absorb a spill of about 1000 mL (volume of one i.v. bag or bottle).
2. Appropriate PPE to protect the worker during cleanup, including two pairs of disposable gloves (one outer pair of heavy utility gloves and one pair of inner gloves); nonpermeable, disposable protective garments (coveralls or gown and shoe covers); and face shield.
3. Absorbent, plastic-backed sheets or spill pads.
4. Disposable toweling.
5. At least two sealable, thick plastic hazardous waste disposal bags (prelabeled with an appropriate warning label).
6. One disposable scoop for collecting glass fragments.
7. One puncture-resistant container for glass fragments.

### Appendix I—Recommendations for Spill Cleanup Procedure

#### General

1. Assess the size and scope of the spill. Call for trained help, if necessary.
2. Spills that cannot be contained by two spill kits may require outside assistance.
3. Post signs to limit access to spill area.
4. Obtain spill kit and respirator.
5. Don PPE, including inner and outer gloves and respirator.
6. Once fully garbed, contain spill using spill kit.
7. Carefully remove any broken glass fragments and place them in a puncture-resistant container.
8. Absorb liquids with spill pads.
9. Absorb powder with damp disposable pads or soft toweling.
10. Spill cleanup should proceed progressively from areas of lesser to greater contamination.
11. Completely remove and place all contaminated material in the disposal bags.
12. Rinse the area with water and then clean with detergent, sodium hypochlorite solution, and neutralizer.
13. Rinse the area several times and place all materials used for containment and cleanup in disposal bags. Seal bags and place them in the appropriate final container for disposal as hazardous waste.
14. Carefully remove all PPE using the inner gloves. Place all disposable PPE into disposal bags. Seal bags and place them into the appropriate final container.
15. Remove inner gloves; contain in a small, sealable bag; and then place into the appropriate final container for disposal as hazardous waste.
16. Wash hands thoroughly with soap and water.
17. Once a spill has been initially cleaned, have the area recleaned by housekeeping, janitorial staff, or environmental services.

#### Spills in a BSC or Isolator

1. Spills occurring in a BSC or isolator should be cleaned up immediately.
2. Obtain a spill kit if the volume of the spill exceeds 30 mL or the contents of one drug vial or ampul.

3. Utility gloves (from spill kit) should be worn to remove broken glass in a BSC or an isolator. Care must be taken not to damage the fixed-glove assembly in the isolator.
4. Place glass fragments in the puncture-resistant hazardous drug waste container located in the BSC or discard into the appropriate waste receptacle of the isolator.
5. Thoroughly clean and decontaminate the BSC or isolator.
6. Clean and decontaminate the drain spillage trough located under the Class II BSC or similarly equipped Class III BSC or isolator.
7. If the spill results in liquid being introduced onto the HEPA filter or if powdered aerosol contaminates the "clean side" of the HEPA filter, use of the BSC or isolator should be suspended until the equipment has been decontaminated and the HEPA filter replaced.

### Appendix J—OSHA-Recommended Steps for Immediate Treatment of Workers with Direct Skin or Eye Contact with Hazardous Drugs<sup>3</sup>

1. Call for help, if needed.
2. Immediately remove contaminated clothing.
3. Flood affected eye with water or isotonic eyewash for at least 15 minutes.
4. Clean affected skin with soap and water; rinse thoroughly.
5. Obtain medical attention.
6. Document exposure in employee's medical record and medical surveillance log.
7. Supplies for emergency treatment (e.g., soap, eyewash, sterile saline for irrigation) should be immediately located in any area where hazardous drugs are compounded or administered.

### Glossary

**Antineoplastic drug:** A chemotherapeutic agent that controls or kills cancer cells. Drugs used in the treatment of cancer are cytotoxic but are generally more damaging to dividing cells than to resting cells.<sup>4</sup>

**Aseptic:** Free of living pathogenic organisms or infected materials.<sup>4</sup>

**Biological-safety cabinet (BSC):** A BSC may be one of several types.<sup>4</sup>

**Class I BSC:** A BSC that protects personnel and the work environment but does not protect the product. It is a negative-pressure, ventilated cabinet usually operated with an open front and a minimum face velocity at the work opening of at least 75 ft/min. A class I BSC is similar in design to a chemical fume hood except that all of the air from the cabinet is exhausted through a high-efficiency particulate air (HEPA) filter (either into the laboratory or to the outside).

**Class II BSC:** A ventilated BSC that protects personnel, the product, and the work environment. A Class II BSC has an open front with inward airflow for personnel protection, downward HEPA-filtered laminar airflow

for product protection, and HEPA-filtered exhausted air for environmental protection.

**Type A1 (formerly type A):** These Class II BSCs maintain a minimum inflow velocity of 75 ft/min, have HEPA-filtered down-flow air that is a portion of the mixed down-flow and inflow air from a common plenum, may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy, and may have positive-pressure contaminated ducts and plenums that are not surrounded by negative-pressure plenums. They are not suitable for use with volatile toxic chemicals and volatile radionucleotides.

**Type A2 (formerly type B3):** These Class II BSCs maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered down-flow air that is a portion of the mixed down-flow and inflow air from a common exhaust plenum, may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy, and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for minute quantities of volatile toxic chemicals and trace amounts of radionucleotides, they must be exhausted through properly functioning exhaust canopies.

**Type B1:** These Class II BSCs maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered down-flow air composed largely of uncontaminated, recirculated inflow air, exhaust most of the contaminated down-flow air through a dedicated duct exhausted to the atmosphere after passing it through a HEPA filter, and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for work involving minute quantities of volatile toxic chemicals and trace amounts of radionucleotides, the work must be done in the directly exhausted portion of the cabinet.

**Type B2 (total exhaust):** These Class II BSCs maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered down-flow air drawn from the laboratory or the outside, exhaust all inflow and down-flow air to the atmosphere after filtration through a HEPA filter without recirculation inside the cabinet or return to the laboratory, and have all contaminated ducts and plenums under negative pressure or surrounded by directly exhausted negative-pressure ducts and plenums. These cabinets may be used with volatile toxic chemicals and radionucleotides.

**Class III BSC:** A BSC with a totally enclosed, ventilated cabinet of gastight construction in which operations are conducted through attached rubber gloves and observed through a nonopening view window. This BSC is maintained under negative pressure of at least 0.50 in of water gauge, and air is drawn into the cabinet through HEPA filters. The exhaust air is treated by double HEPA filtration or single HEPA filtration-incineration. Passage of materials in and out of the cabinet is generally performed through a dunk tank (accessible through the cabinet floor) or a double-door

pass-through box (such as an autoclave) that can be decontaminated between uses.

**Chemotherapy drug:** A chemical agent used to treat diseases. The term usually refers to a drug used to treat cancer.<sup>4</sup>

**Chemotherapy glove:** A medical glove that has been approved by FDA for use when handling antineoplastic drugs.<sup>4</sup>

**Chemotherapy waste:** Discarded items such as gowns, gloves, masks, i.v. tubing, empty bags, empty drug vials, needles, and syringes used while preparing and administering antineoplastic agents.<sup>4</sup>

**Closed system:** A device that does not exchange unfiltered air or contaminants with the adjacent environment.<sup>4</sup>

**Closed-system drug-transfer device:** A drug-transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system.<sup>4</sup>

**Cytotoxic:** A pharmacologic compound that is detrimental or destructive to cells within the body.<sup>4</sup>

**Deactivation:** Treating a chemical agent (such as a hazardous drug) with another chemical, heat, ultraviolet light, or another agent to create a less hazardous agent.<sup>4</sup>

**Decontamination:** Inactivation, neutralization, or removal of toxic agents, usually by chemical means.<sup>4</sup> Surface decontamination may be accomplished by the transfer of hazardous drug contamination from the surface of a nondisposable item to disposable ones (e.g., wipes, gauze, towels).

**Disinfecting:** Removal of viable organism from surfaces using 70% alcohol or other appropriate disinfectant prior to compounding of sterile hazardous drugs.

**Engineering controls:** Devices designed to eliminate or reduce worker exposures to chemical, biological, radiological, ergonomic, or physical hazards. Examples include laboratory fume hoods, glove bags, retracting syringe needles, sound-dampening materials to reduce noise levels, safety interlocks, and radiation shielding.<sup>4</sup>

**Genotoxic:** Capable of damaging DNA and leading to mutations.<sup>4</sup>

**Glove box:** A controlled environment work enclosure providing a primary barrier from the work area. Operations are performed through sealed gloved openings to protect the worker, the ambient environment, and/or the product.<sup>4</sup>

**Hazardous drug:** Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low doses in humans or animals, genotoxicity, and new drugs that mimic existing hazardous drugs in structure or toxicity.<sup>4</sup>

**Hazardous waste:** Any waste that is an RCRA-listed hazardous waste [40 C.F.R. 261.30-.33] or that meets an RCRA characteristic of ignitability, corrosivity, reactivity, or toxicity as defined in 40 C.F.R. 261.21-.24.<sup>4</sup>

**Health care settings:** All hospitals, medical clinics, outpatient facilities, physicians' offices, retail pharmacies, and similar facilities dedicated to the care of patients.<sup>4</sup>

**Health care workers:** All workers who are involved in the care of patients. These include pharmacists, pharmacy technicians, nurses (registered nurses, licensed prac-

tical nurses, nurses' aides, etc.), physicians, home health care workers, and environmental services workers (housekeeping, laundry, and waste disposal).<sup>4</sup>

**HEPA filter:** Filter rated 99.97% efficient in capturing particles 0.3- $\mu$ m in diameter.<sup>4</sup>

**Horizontal-laminar-airflow hood (horizontal-laminar-airflow clean bench):** A device that protects the work product and the work area by supplying HEPA-filtered air to the rear of the cabinet and producing a horizontal flow across the work area and out toward the worker.<sup>4</sup>

**Isolator:** A device that is sealed or is supplied with air through a microbially retentive filtration system (HEPA minimum) and may be reproducibly decontaminated. When closed, an isolator uses only decontaminated interfaces (when necessary) or rapid transfer ports for materials transfer. When open, it allows for the ingress and egress of materials through defined openings that have been designed and validated to preclude the transfer of contaminants or unfiltered air to adjacent environments. An isolator can be used for aseptic processing, for containment of potent compounds, or for simultaneous asepsis and containment. Some isolator designs allow operations within the isolator to be conducted through a fixed-glove assembly without compromising asepsis or containment.<sup>4</sup>

**Aseptic isolator:** A ventilated isolator designed to exclude external contamination from entering the critical zone inside the isolator.<sup>4</sup>

**Aseptic containment isolator:** A ventilated isolator designed to meet the requirements of both an aseptic isolator and a containment isolator.<sup>4</sup>

**Containment isolator:** A ventilated isolator designed to prevent the toxic materials processed inside it from escaping to the surrounding environment.<sup>4</sup>

**Laboratory coat:** A disposable or reusable open-front coat, usually made of cloth or other permeable material.<sup>4</sup>

**Material safety data sheet:** Contains summaries provided by the manufacturer to describe the chemical properties and hazards of specific chemicals and ways in which workers can protect themselves from exposure to these chemicals.<sup>4</sup>

**Mutagenic:** Capable of increasing the spontaneous mutation rate by causing changes in DNA.<sup>4</sup>

**Personal protective equipment (PPE):** Items such as gloves, gowns, respirators, goggles, and face shields that protect individual workers from hazardous physical or chemical exposures.<sup>4</sup>

**Respirator:** A type of PPE that prevents harmful materials from entering the respiratory system, usually by filtering hazardous agents from workplace air. A surgical mask does not offer respiratory protection.<sup>4</sup>

**Risk assessment:** Characterization of potentially adverse health effects from human exposure to environmental or occupational hazards. Risk assessment can be divided into five major steps: hazard identification, dose-response assessment, exposure assessment, risk characterization, and risk communication.<sup>4</sup>

**Surface decontamination:** Transfer of hazardous drug contamination from the surface of nondisposable items to disposable ones (e.g., wipes, gauze, towels). No procedures have been studied for surface decontamination of hazardous drug contaminated surfaces. The use of gauze moistened with alcohol, sterile water, peroxide, or sodium hypochlorite solutions may be effective. The disposable item, once contaminated, must be contained and discarded as hazardous waste.

**Ventilated cabinet:** A type of engineering control designed for purposes of worker protection (as used in these guidelines). These devices are designed to minimize worker exposures by controlling emissions of airborne contaminants through (1) the full or partial enclosure of a potential contaminant source, (2) the use of airflow capture velocities to capture and remove airborne contaminants near their point of generation, and (3) the use of air pressure relationships that define the direction of airflow into the cabinet. Examples of ventilated cabinets include BSCs, containment isolators, and laboratory fume hoods.<sup>4</sup>

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Developed through the ASHP Council on Professional Affairs and approved by the ASHP Board of Directors on January 12, 2006.

These guidelines supersede the ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs (*Am J Hosp Pharm.* 1990; 47:1033-49).

LUCI A. POWER, M.S., is gratefully acknowledged for leading the revision of these guidelines. ASHP acknowledges the following individuals for their contributions to these guidelines: Thomas H. Connor, Ph.D., CAPT (ret.) Joseph H. Deffenbaugh Jr., M.P.H., CDR Bruce R. Harrison, M.S., BCOP, Dayna McCauley, Pharm.D., BCOP, Melissa A. McDiarmid, M.D., M.P.H., Kenneth R. Mead, M.S., PE, and Martha Polovich, M.N., RN, AOCN.

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The bibliographic citation for this document is as follows: American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63:1172-93.