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Biological Safety Cabinets (BSCs) for Sterile Hazardous Drug Compounding:

Information to Consider Before Choosing an A2 versus B2

Those organizations deciding to include a Class II biological safety cabinet (BSC) in their operations often narrow the choice to either an A2 or a B2. Making this decision can be difficult and may depend in large part upon whether the BSC is being integrated into an existing or new and not yet built facility. The ASHP Guidelines on Handling Hazardous Drugs[1] provide a thoughtful and detailed discussion about C-PECs and should be part of any examination of this topic. It provides a comprehensive rationale and recommendations for all aspects of hazardous drug handling, exhaustive references from primary sources, and recommendations for the use of Class II BSCs and Class III BSCs, as well as Compounding Aseptic Containment Isolators (CACIs).

Though both Class II Types A2 and B2 are compliant with USP 800, Type B2 has been the gold standard in hazardous drug (HD) sterile compounding operations that compound drugs with the potential to volatilize. These types of BSCs exhaust 100% of air externally without recirculation while providing ISO Class 5 conditions where unidirectional first air bathes critical sites, thereby reducing the potential for microbial contamination. However, it is sometimes impractical or exceedingly difficult to integrate these cabinets into what may be less-than-ideal pharmacy cleanroom suites. Though worker protection is always of the utmost concern, the cost to operate a B2 is significantly higher than other available BSCs.

This Pearl is intended to help pharmacies weigh evidence and perspectives so they can determine which BSC is best suited for their personnel and operations. It provides a cursory review of some HD contamination attributes and changes in HD pharmacy sterile compounding practice, as well as the operational considerations (cost impacts, ventilation effectiveness, and facility integration) in the comparison of these two types of Class II BSCs.

Realities of Hazardous Sterile Compounding Pharmacy Practice

HD contamination has been found both inside HD compounding areas and inside containment primary engineering controls (C-PECs). Researchers have determined that the outside of drug vials, as well as their primary packaging, is contaminated with low levels of hazardous drug contamination.[2,3] Certain drugs, including cisplatin, cyclophosphamide, and fluorouracil, have been shown to evaporate and form a gas phase (volatilize) during normal handling.[4] Kiffmeyer and associates said other hazardous drugs have similar vapor pressures, and therefore many untested drugs are also likely to volatilize.

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[1] Power LA and Coyne JW. ASHP Guidelines on Handling Hazardous Drugs. Am J Health-Syst Pharm. 2018. 75(24):1996-2031.
[2] Hedmer M et al. Surface Contamination of Cyclophosphamide Packaging and Surface Contamination with Antineoplastic Drugs in a Hospital Pharmacy in Sweden. Annals. 2005.
[3] Connor TH, Sessink PJ, Harrison BR et al. Surface contamination of chemotherapy drug vials and evaluation of new vial-cleaning techniques: results of three studies. Am J Health Syst Pharm. 2005. 62:475-84.
[4] Kiffmeyer TK, Kube C et al. Vapour pressures, evaporation behavior and airborne concentrations of hazardous drugs: Implications for occupational safety. The Pharmaceutical Journal. 2002. (268): 331-7.

Since the drugs mentioned above are three very commonly used HDs, it may be simpler to consider that many drugs for which there is no data, may, in fact, volatilize.

Based on CriticalPoint's compliance study data from 2017 to 2019, the use of closed system drug-transfer devices (CSTDs) in HD sterile compounding may be on the rise. It certainly seems like USP 800's requirement for pharmacies to dispense the final dose ready for administration with a CSTD attached if the dosage form permits may be a driving factor. In some modeling CriticalPoint has performed, manual negative-pressure compounding techniques significantly increase the time it takes to prepare one HD CSP. The use of vapor capture CSTDs during the compounding process may well reduce the burden of HD vapor and liquid contamination in C-PECs.

Common Characteristics of Biological Safety Cabinets

Class II BSCs have a common function and design but operate differently. The internal design of a BSC creates product and environmental protection through the integration of HEPA filters and blower motors located in the cabinet's plenum (the interior of the cabinet). The difference is how each type of BSC moves air. This may be by recirculating the air it creates through balance and air distribution or by totally exhausting all air it created internally. There are two different applications that are appropriate for Class II BSCs.

1. *Fully recirculating BSCs:* The supply HEPA filter provides downward unidirectional airflow for CSP protection, while the exhaust HEPA filter provides personnel protection by drawing air in the front of the cabinet. This ensures containment. Then the air is exhausted out of the cabinet back into the room. This type is appropriate for nonhazardous drug applications.
2. *Containment primary engineering controls (C-PECs):* These types of BSCs are designed to protect the final CSP from microbial contamination while simultaneously protecting compounding personnel from exposure to HDs when properly externally ventilated. Since some HDs volatilize at room temperature and HEPA filters work to filter particulates (not vapors), these BSCs must be externally vented outside of the building.

Requirements and Use of C-PECs per USP Chapter 800

Prior to USP Chapter 800, cleanroom designers and certifiers asked pharmacies to perform a "risk assessment" to determine the exposure danger to HD vapors and residues based on the drugs they anticipated compounding at the location. Though this request seemed to make sense, it wasn't practical because information about the volatility of drugs being compounded was not widely available or easily understood. USP 800 requires external ventilation of C-PECs to ensure worker safety since no safe level of HD exposure has been established. So, the primary goal of externally vented C-PECs is to safely and effectively remove hazardous drug vapors while ensuring an appropriate ISO 5 environment for sterile compounding. If a C-PEC is not externally exhausted and it is used to compound HDs, an evaluation must be conducted to determine if it is possible to install an appropriate duct connection to the existing BSC. Due to the age or capabilities of the current BSC, the purchase of a new BSC that satisfies the requirements of external ventilation may be required. Work with a mechanical engineer for external ventilation and the BSC manufacturer to determine the appropriate exhaust connection and whether retrofit is possible.

Table 1: Appropriate BSCs for Sterile Hazardous Compounding and the Design Capability of Each Type

Equipment Type	Ventilation		Non-Hazardous Application	Hazardous Application	Externally Exhausted	Exhaust Volume* Avg. for 4' BSC
	Approximate % of HEPA-Filtered Exhaust Air	Approximate % of Recirculated HEPA-Filtered Air				
Class II Type A2	30%	70%	Yes	Yes	Exhausted or recirculating	300 to 400
Class II Type B2	100%	None	Yes	Yes	Required	650 to 850

** In cubic feet per minute (CFM) and the value may vary between manufacturers*

Facility and C-PEC External Ventilation Challenges

Exhausting a BSC is not as simple as installing a duct connection to the BSC and a blower motor on the roof. Engineers need to know the specific amount and volume of exhaust to determine the appropriate exhaust setup for each cabinet and to integrate them into the facility properly. These are some of the factors that must be considered and are discussed in more detail.[5]

- static pressure requirements of the duct
- length of the exhaust duct
- required values for operation and concurrent balance values from the manufacturer
- secondary engineering control (cleanroom suite) and C-PEC integration balance
- HEPA filter particulate loading

Duct static pressure is the amount of constant airflow flowing through a duct system at any given distance. The duct pressure constant is the strength of drawing power and how constantly the drawing power is maintained. The distance from the BSC to the exhaust discharge point on the roof can affect duct pressure constants. The longer the duct line is from the cabinet to the end discharge, the higher the duct pressure constant is required to be to maintain a specific value determined to be needed. Duct pressure constants can also be affected by multiple BSCs sharing a common duct line by being ganged together. This creates a challenge for each BSC to maintain the individual parameters required to operate.

All BSC manufacturers provide necessary airflow values for their BSC to operate when externally vented. The engineer takes that value and the facility parameters (such as cubic feet of room, desired air changes per hour, etc.) to calculate the size and capability requirements for the exhaust system. However, that is not as simple as it sounds. Often, the design and balance of the BSC exhaust values do not relate to the required values to maintain the operation of a C-PEC during certification, which can lead to inadequate exhaust airflow. The installation, design, and balance values of the BSC are higher than the operational certification values. The engineer must recognize the differences in these values by referring to the manufacturer's concurrent balance value (CBV) and not the operational exhaust parameters to design an exhaust system that will successfully maintain both exhaust requirements and operational exhaust values when integrating a Type B2 BSC into a facility.

[5] Gilpin R and Powitz R. NSF International NSF 49-2018 Annex E. Biosafety Cabinet Selection, Installation, Use, Lifespan, and Decommissioning. 2018. Retrieved 11/5/19.

The cleanroom suite or containment segregated compounding area (C-SCA) itself is challenged during the integration of an exhausted BSC. The type of Class II BSC determines how much supply-and-exhaust/return air is applied to balance the room's air changes per hour (ACPH), room-to-room pressure, temperature, and humidity. The existing HVAC may not be enough to accommodate certain exhausted BSCs. The facility HVAC may require additional help to make up for the additional load on the system to integrate BSCs that require larger amounts of exhaust air and will contribute to additional costs across the facility. Therefore, it's essential to understand what the cause and effect can be based on the type of Class II BSC selected.

It is also important to understand the factors involved in integrating a BSC into the existing or planned exhaust system. Since HEPA filters trap particulates while providing filtered air, particulates build and accumulate in the filter's pleats. This is known as filter loading. The issue with filter loading is that it is not always accounted for in brand-new facilities or in an exhaust system design. As the HEPA filters load, it is harder for the exhaust system to maintain its design parameters. The exhaust motor's revolutions per minute (RPM) increase to compensate for filter loading. The motor may be beyond its capability at the first sign of filter loading. A loading filter can affect the facility's HVAC, exhaust blower and output design, as well as the overall duct static pressure. Due to these variables, the engineer must design an exhaust system to accommodate anticipated filter loading. This is accomplished by designing the functionality of the exhaust on the half-life of the HEPA filter and the type of BSC. By using the manufacturer-provided values to calculate the additional needed airflow value to provide exhaust increments as the HEPA filters load, the design plan is more practical and likely to work as the facility ages.

Table 2: Expected Cost and Facility Impact of Different Class II BSCs

Equipment Type	Estimated Exhaust Installation Cost	Estimated Maintenance Cost (parts, service & HEPA filters)	Estimated Annual Operating Cost	Estimated Total Cost	Energy Usage and Facility Impact	Estimated Filter Loading
Class II Type A2	<$25,000	<$5,000	<$40,000	<$70,000	Moderate	Low
Class II Type B2	<$35,000	<$6,000	<$75,000	<$116,000	High	High

Class II Type A2 Cabinets

A2 cabinets recirculate approximately 70% of the air they create through HEPA filters and exhaust 30% of the air. These canopy-connected devices typically require half the exhaust volume of a B2 BSC, making them more cost-efficient. Maintaining a microbial state of control through pressure balance and air change rates in the C-SECs is easier to achieve with A2 BSCs. Because A2 cabinets require less exhaust to operate, less replacement air is needed for the C-SEC. A BSC requiring a larger amount of exhaust makes the room overly negative, and the replacement air needed to balance the space often exceeds the ability of the existing HVAC system.

Also, the relative pressure relationships inside the cleanroom suite may benefit from having A2 cabinets because the pressure balance can be adjusted more easily. If multiple A2 cabinets require external ventilation, they can be ganged together on the same properly designed exhaust stack without issue.

Exhausted A2 BSCs also tolerate airflow fluctuations that naturally occur in duct lines and do not require the strong constant duct pressure that B2s need to operate correctly.

Class II Type B2 Cabinets

B2 cabinets have traditionally been preferred by professional organizations such as the National Institute for Occupational Safety and Health (NIOSH), the Hematology/Oncology Pharmacy Association (HOPA), the International Society of Oncology Pharmacy Practitioners (ISOPP), and the Canadian Association of Pharmacy in Oncology (CAPhO). Since volatility (or not) cannot always be determined, the B2s were preferred because air does not recirculate in the cabinet, and any potential vapor generation during compounding is exhausted immediately outside of the building. Some of the consequences of this design include that:

- B2 cabinets require more exhaust energy than any other cabinet, leading to energy inefficiencies and increased operating costs.
- B2 cabinets also require a strong duct static pressure because the cabinet cannot maintain operation consistently in the face of duct pressure fluctuations.
- When multiple B2 cabinets share the same exhaust, they usually fight each other for exhaust constants, leading to insufficient airflow or significant pressure balance system errors with the shared BSCs and the C-SECs.

Ideally, each B2 cabinet should be connected to its own dedicated exhaust system, which allows each B2 to operate effectively, albeit with increased energy cost and challenge to the facility HVAC system. The system's airflow must be enough to replace and balance the increased negative pressures in the C-SEC.

Worker Protection Effectiveness and Safety Concerns

Case studies may be found in the public domain about exhausted biological safety cabinets used for sterile hazardous compounding. This information varies widely based on when the articles were written and the opinions of the authors about which BSC is best based on safety and facility concerns. In many organizations, B2 cabinets are used for highly volatile toxic chemicals or volatile radionucleotides as required by governing bodies. But recent literature is beginning to evaluate if an exhausted Class II Type A2 BSC used for HD sterile compounding contains and exhausts vapors and aerosols as effectively as a B2 BSC.[6] The authors compared an A2 and B2 cabinets installed in pharmacy settings. During the study, they performed prequalification tests to ensure that the cabinets were correctly installed and were operating correctly. Containment capabilities of each type of unit were performed using tracer gas and, again, using cyclophosphamide (a drug that volatilizes) sampling during actual sterile compounding. Results of this head-to-head comparison showed that the A2 BSC was able to contain the tracer gas and air containing cyclophosphamide just as well as the B2.

The NIOSH Alert states that if A2 cabinets are used for "minute quantities of volatile toxic chemicals and trace amounts of radionucleotides, they must be exhausted through properly functioning exhaust canopies."[7] Based on the increasing use of vapor capture CSTDs and the testing already described, it would seem the amount of residue inside and vapor generated during compounding is very low.

[6] Taylor AV, Baker N, Hulsey M et al. Evaluating containment effectiveness of A2 and B2 biological safety cabinets. American Journal of Health-System Pharmacy. 76(9): 599-607. May 1, 2019.

[7] Department of Health and Human Services. Centers for Disease Control. National Institute for Occupational Safety and Health. NIOSH Alert Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. DHHS Publication Number 2004-165. September 2004. p. 43. Retrieved 11/12/19.

The NIOSH Alert also states "the Type B2 is preferred, but A2 and B1 cabinets are allowed under certain conditions,"[8] which includes not using "a ventilated cabinet *that recirculates air inside the cabinet or exhausts air back into the room environment unless the hazardous drug(s) in use will not volatilize (evaporate) while they are being handled or after they are captured by the HEPA filter*.[8]

In a letter to James T. Wagner dated November 28, 2007, Kenneth R. Mead MS, PE and Senior Research Engineer of the Control Technology Team at the U.S. Public Health Service, stated his general agreement with this conclusion. He said that "at a minimum, ventilation rate of 30 air changes per hour within the pharmacy, the high ventilation rate for the pharmacy in which the BSCs are located, should serve to quickly dilute any contaminant potentially escaping from the BSC."[9] He also stated that that small amount of chemotherapy drugs believed to escape during the compounding process would be expected to meet the definition of minute quantities and that the use of the A2 cabinet is a reasonable candidate to meet the "under certain conditions" use guideline in the NIOSH Alert.

All Class II BSCs discussed earlier have been approved for use with small volumes of volatile materials but were principally designed for microbiological containment and asepsis. The B2 cabinet does not offer any additional personnel or environmental protection compared to the A2. The only advantage provided by the B2 cabinet is that the volatile materials will be immediately evacuated from the work area without recirculation. The other designs will recirculate air internally prior to exhausting it outside of the cabinet.

From an exhaust performance perspective, all exhausted Class II BSCs must have audible and visual alarms that can detect duct system errors and notify the worker in the event of a loss of containment. However, a canopy-connected A2 cabinet that experiences a loss of containment partially mitigates the airflow in the event of roof exhaust motor failure by allowing the remaining duct air to pass through the gaps designed at the canopy connection and not flow back into the BSC exposing the worker to HD contamination. A B2 cabinet must be hard-connected to the exhaust duct without gaps at the connection. If the BSC's interlock safety feature is not set up and verified correctly (as required) and a loss of containment occurs, the unit cannot properly prevent the exhaust air from flowing back into the cabinet, thus exposing the worker to HD contamination.

How to Decide Which BSC Meets Your Needs

Choosing the BSC best suited for each pharmacy's sterile compounding operation may be determined by a variety of factors, and it is the pharmacy's responsibility to use its professional judgment to make that determination. These are the specific factors that must be evaluated:

1. **Physical plant:** Will the BSC be integrated into an existing facility and HVAC system, or is it selected for a facility that has not yet been built?
2. **Budget:** Energy savings and overall project costs are always a concern, and an understanding of how BSC types can affect those variables provides insight into potential budget savings without sacrificing worker protections.
3. **USP 800**: USP 800 is now compendially applicable. All C-PECs must be exhausted externally, but they also must be carefully integrated into each facility.

[8] Department of Health and Human Services. Centers for Disease Control. National Institute for Occupational Safety and Health. NIOSH Alert Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. DHHS Publication Number 2004-165. September 2004. p. 15. Retrieved 11/12/19.
[9] Personal correspondence. Kenneth R. Mead to James T. Wagner. November 28, 2007.

4. **Specific hazardous drugs compounded:** Try to identify the volatility of the drugs that are or will be compounded in the future.
5. **CSTD use and type:** Use of CSTDs cleared by the FDA under product code ONB[10] with proper use, work to ensure generation of only the most minute amounts of hazardous drugs while simultaneously increasing worker efficiency.

Ultimately it is the responsibility of the pharmacy to evaluate its physical plant, the volatility of the drugs compounded, and their compounding processes to determine the BSC that most appropriately meets its needs. Careful of review of USP Chapter 800 and any relevant state-specific regulations, as well as the information contained in the ASHP Guidelines on Handling Hazardous Drugs should provide a basis for decision-making. Seek guidance from others and engage a qualified expert with demonstrated expertise in designing, building, and using compounding facilities appropriate for sterile hazardous drug compounding.

[10] Power LA and Coyne JW. ASHP Guidelines on Handling Hazardous Drugs. Am J Health-Syst Pharm. 2018. 75(24). Page 2006.