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Evaluating Six Commercially Available Closed-System Drug-Transfer Devices Against NIOSH's 2015 Draft Vapor Protocol

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Abstract

Purpose: In 2015, the National Institute for Occupational Safety and Health (NIOSH) published a draft vapor containment protocol to quantitatively evaluate combined liquid, aerosol, and vapor containment performance of commercially available closed-system drug-transfer devices (CSTDs) that claim to be effective for gas/vapor containment within a controlled test environment. Until the release of this proposed protocol, no standard method for evaluating airtightness of CSTDs existed. The aim of this study was to evaluate six commercially available CSTDs utilizing NIOSH draft protocol methodology to evaluate vapor containment under a robust vapor challenge. **Methods:** In this study, six commercially available CSTDs were tested utilizing draft NIOSH vapor containment protocol methodology to simulate drug compounding and administration using 70% isopropyl alcohol (IPA) as the challenge agent. All device manipulations were carried out in an enclosed test chamber. A Miran sapphIRe gas analyzer was used to detect IPA vapor levels that escaped the device. Study test included the two tasks designated by the NIOSH protocol, with additional steps added to the evaluation. Tasks were repeated 10 times for each device. **Results:** Only three of the six tested CSTDs (Equashield®, HALO®, and PhaSeal™) had an average IPA vapor release below the quantifiable performance threshold (1.0 ppm) for all tasks performed. This value was selected by NIOSH to represent the performance threshold for successful containment. The remaining three CSTDs had vapor release above 1 ppm at various times during the IPA manipulation process. **Conclusion:** Equashield®, HALO®, and PhaSeal™ devices tested met the 2015 NIOSH protocol quantifiable performance threshold, functioning as a truly closed system. Quantifiable effective data may be useful in product selection.

Keywords

CSTD, hazardous drugs, NIOSH, vapor release, health care workers, occupational exposure

Introduction

Exposure to hazardous drugs (HDs) including antineoplastic agents has been associated with adverse health outcomes including reproductive toxic effects and cancer.[1] While many health care workers can be at risk of HD occupational exposure,[2,3] pharmacists, pharmacy technicians, and nurses are most likely to be exposed,[3] especially throughout the preparation or administration process.[4]

Dermal contact with HD-contaminated surfaces is the primary route of occupational exposure, and have the predominant role in the HD uptake by health care personnel,[5,6] as evidenced by drug excretion in health care worker urine samples.[7] Several environmental wipe sampling studies have demonstrated widespread surface contamination including the outer surface of syringes, drug vials, and preparation and administration areas.[8-18] To limit this exposure and protect health care workers, safe HD-handling guidelines have been incorporated such as a biological safety cabinet (BSC) and personal protective equipment (eg, gloves, gowns, mask).[1,19-21] However, studies show that occupational exposure still occurs despite the use of these protective guidelines.[3,22-26] Furthermore, detection of measurable concentrations of HDs from urine samples of exposed workers implies that drug absorption still occurs.[2,26]

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Table 1. CSTD Components Used for Testing.

Manufacturer and name of CSTD	Vial access device	Syringe access device	Bag access device	Line access device
B. Braun and Teva Medical-OnGuard™ with Tevadaptor®	Tevadaptor Vial Adaptor, 412111	Tevadaptor Syringe Adaptor, 412118	Tevadaptor Spike Port Adaptor, 412113	Tevadaptor Secondary Connecting Set with ULTRASITE Needlefree Valve, 412116
BD Carefusion-PhaSeal™	Protector, P50	Injector Luer Lock, N35	Infusion Adaptor, C100	Connector Luer Lock, C45
BD CareFusion-Texium™ with SmartSite™ VialShield	SmartSite™ VialShield 20mm Closed Vial Access Device, MV0520	Bonded Syringe with Texium 60mL, MY8060	Secondary Set Non-Vented with Texium, 10013364T	Alaris Primary Tubing, 2420-0500
Corvida Medical-HALO®	Closed Vial Adaptor, CVA200	Closed Syringe Adaptor, CSA100	Closed Bag Adaptor, CBA100	Closed Line Adaptor, CLA100
Equashield-Equashield®	Vial Adaptor 20, VA-20	Syringe Unit 60, SU-60	Spike Adaptor, SA-1	Luer Lock Adaptor, LL-2
ICU Medical- ChemoLock™	Locking Universal Vented Vial Access Device, CL-70	Spinning ChemoLock, CL-2000S	ChemoLock Bag Spike, CL-10	ChemoLock Port, CL-2100

Note. CSTD = closed-system drug-transfer device.

The closed-system drug-transfer device (CSTD) was first defined by the 2004 NIOSH alert as a device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of HD or vapor concentrations outside the system.[1] The NIOSH alert and the United States Pharmacopeia, the 2008 revision of Chapter <797> Pharmaceutical Compounding—Sterile Preparations, recommended CSTD use in conjunction with other safe-handling guidelines.[1,27] CSTDs offer additional protection by limiting the potential for drug aerosol contamination to further reduce exposure risks.[28] The recent USP <800> Hazardous Drugs—Handling in Healthcare Settings, augments USP <797> (2008) and while supporting compounding recommendations, mandates CSTD use for HD administration when the dosage form allows.[28] Several studies have shown CSTD benefits (vs no CSTD) in reducing drug uptake, excretion, and worksite surface contamination with HD residues.[29-38] A variety of CSTD models are available, providing multiple options for health care facilities and pharmacies. CSTDs are generally available in two design types: (1) one that uses a physical barrier to prevent all mass from crossing the system boundary or (2) one that uses air-cleaning or filtration technologies to specifically prohibit environmental contaminants and HD concentrations from crossing the system.[39] While there are no performance standards comparing CSTDs for drug containment, the selection of a product now relies primarily on cost and claimed protection performance. USP <800> states there is no evidence that all CSTDs will perform equally.[28]

In August 2015, NIOSH released a proposed draft protocol to quantitatively evaluate combined liquid, aerosol, and vapor containment performance of the barrier-type, commercially available CSTDs within a controlled test environment.[39] Developing a quantitative universal test protocol provides additional information about individual product performance, which may aid practitioners in making more informed product selection. NIOSH developed this draft protocol, using 70% isopropyl alcohol (IPA) as a robust challenge agent to evaluate vapor release by CSTDs.[39] The objective of this study was to test six currently available CSTDs, not only physical-barrier types, using the testing method as described in the 2015 NIOSH vapor containment performance draft protocol and adding modest modifications to the test. It's important to know the degree to which any CSTD can maintain containment when faced with a robust vapor challenge.

Methods

Materials and Procedures

To compare and evaluate vapor containment using IPA as the challenge agent described in the 2015 NIOSH draft protocol, six commercially available CSTD devices (ChemoLock™, Equashield®, HALO®, OnGuard™ with Tevadaptor®, PhaSeal™, Texium™ with SmartSite™ VialShield) were tested.

All components tested were non-expired products procured through commercial channels and used as instructed by the manufacturers (Table 1).

The tests were conducted within a closed Bel-Art Techni-Dome 360 Glove Chamber with neoprene gloves (Bel Art, SP Scienceware, and HB Instruments homepage, available at: https://www.belart.com/techni-dome-360-glove-box-chamber.html). Chamber volume was approximately 4000 cu in, which was smaller than the version used in the NIOSH performance test as the extender "extension piece" was not utilized (Figure 1). The NIOSH test was performed using the dome extender

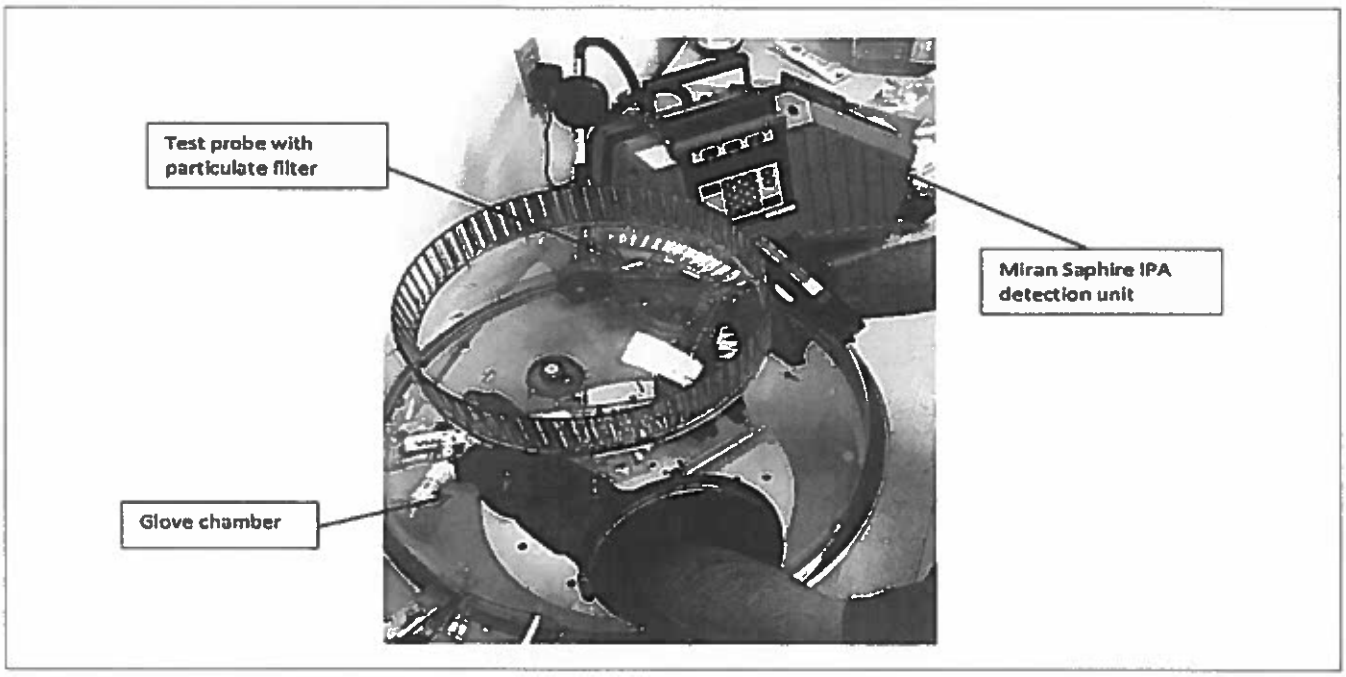

Figure 1. Picture of IPA test setup.
Note. IPA = isopropyl alcohol.

(12" by 20.5" diameter). The extender would have added 3961 cu in of volume to the chamber used in the study. Therefore, measured values were adjusted accordingly.

The IPA detector used to measure IPA vapor that escaped during all manipulations was the Miran SapphIRe (Thermofisher Scientific Homepage, available at: https://www.thermofisher.com/order/catalog/product/205BDL) gas detection unit with a reliable and reproducible level of detection (LOD) of 0.33 ppm in typical ambient air specific for IPA (Figure 1). The flow rate of the instrument was approximately 14 L/min. The equipment was calibrated per the manufacturer's recommendations. NIOSH proposed using 3.33 times the LOD (a common analytical practice) to calculate the analytical limit of quantification (LOQ; ~1.0 ppm), represents the performance threshold for successful containment.

CSTD evaluations were performed utilizing the NIOSH draft protocol (CDC-2015-0075) during compounding (task 1) and administration (task 2). In this study, additional steps were added to task 2 as an extension. The added steps challenged the ability of the device septa to reseal after repeated connections/disconnections. The entire procedure (task 1, task 2, and added steps) was executed 10 times for each of the six devices using new connectors for each repetition (see Tables 2-4). All initial testing conditions were created in accordance with the NIOSH protocol, including ventilation and zeroing of the Miran device as well as vial preparation. Vials (100 ml, 20 mm neck) were prepared and filled with 50 ml 70% IPA (40 vials per CSTD). All CSTD components and supplies required for the test were prepared and placed on a tray inside the Glove Chamber (Bel-Art Techni-Dome) before the start of each task. As described in the NIOSH protocol, task 1 simulated dose compounding (Table 2) while task 2 simulated both compounding and administration (Table 3). The CSTD components evaluated under task 1 included two vial adapters, two syringe adapters, and one bag adapter (Table 2). When Task 1 was completed, the environmental test chamber was opened and all supplies and trays were removed to allow the IPA detector to stabilize to background levels before proceeding to Task 2 and the added steps. The additional steps went beyond the NIOSH protocol and were performed without opening the environmental test chamber or stabilizing the IPA detector to background by using the same components from task 2 (Table 4). The CSTD components evaluated under task 2 plus the additional steps included two vial adapters, two syringe adapters, one bag adapter, and one intravenous port or line adapter.

Vapor levels were recorded with the Miran SafIIRe during task 1 and task 2 plus the added steps in real time after a number of specific steps as in the NIOSH protocol. The NIOSH tasks included several steps, but only 30 steps had measurements (14 steps in task 1, 16 steps in task 2, and six additional steps added to the test) for a total of 36 steps. Readings were taken at the end of each of those steps. All 36 steps were repeated 10 times for each device (see Tables 2-4).

Table 2. Task 1 Steps in the CSTD Study Protocol That Had Measured Values of Vapor Levels Taken at the End of Each Step.

Steps	Task 1—Simulated reconstitution (compounding)
1	Attach VAs to two vials of 70% IPA
2	Connect SA1 to syringe #1 then Connect SA1 to VA1
3	Withdraw 45 ml of IPA from vial #1. Disconnect SA1 from VA1
4	Connect SA1 to VA2
5	Transfer content of syringe #1 (45 ml IPA) to vial #2. Withdraw 45 ml of air from vial #2 into syringe #1
6	Disconnect SA1 from VA2
7	Reconnect SA1 to VA2 and inject 45 ml of air then withdraw 45 ml of IPA. Disconnect SA1 from VA2
8	Connect SA1 to BA and inject 45 ml of IPA into IV bag
9	Disconnect SA1 from BA
10	Connect SA2 to syringe #2, Connect SA2 to VA2
11	Inject air from syringe #2 to VA2, withdraw 45 ml of IPA from vial #2
12	Disconnect SA2 from VA2
13	Connect SA2 to BA and inject 45 ml of IPA into IV bag
14	Disconnect SA2 from BA

Note. CSTD = closed-system drug-transfer device; VA = vial adaptor; IPA = isopropyl alcohol; SA = syringe adaptor; IV = intravenous; BA = bag adaptor.

Table 3. Task 2 Steps in the CSTD Study Protocol That Had Measured Values of Vapor Levels Taken at the End of Each Step.

Steps	Task 2—Simulated reconstitution/administration
1	Attach VAs to two vials of 70% IPA
2	Connect SA3 to syringe #3 then connect SA3 to VA3
3	Withdraw 45 ml of IPA from vial #3. Disconnect SA3 from VA3
4	Connect SA3 to VA4
5	Transfer content of syringe #3 (45 ml IPA) to vial #4. Withdraw 45ml of air from vial #4 into syringe #3
6	Disconnect SA3 from VA4
7	Reconnect SA3 to VA4 and inject 45 ml of air then withdraw 45 ml of IPA. Disconnect SA3 and VA4
8	Connect SA4 to syringe #4. Connect SA4 to VA4
9	Inject air from syringe #4 to VA4. Withdraw 45ml of IPA from vial #4
10	Disconnect SA4 and VA4
11	Connect SA3 to LA
12	Inject IPA (45 ml) into infusion set (connected to IV bag)
13	Disconnect SA3 and LA
14	Connect SA4 from LA
15	Inject IPA (45 ml) into infusion set (connected to IV bag)
16	Disconnect SA4 from LA

Note. CSTD = closed-system drug-transfer device; VA = vial adaptor; IPA = isopropyl alcohol; SA = syringe adaptor; IV = intravenous; LA = line adaptor.

Table 4. Additional Steps in the CSTD Study Protocol That Had Measured Values of Vapor Levels Taken at the End of Each Step.

Steps	Additional steps added as a continuation to Task 2
1	Connect SA3 to VA3, withdraw 5 ml of IPA then disconnect
2	Connect SA3 to VA4, withdraw 5 ml of IPA then disconnect
3	Reconnect SA3 to VA4, transfer 10 ml IPA from syringe#3 to Vial #4 then disconnect
4	Reconnect SA3 and VA4, withdraw 10 ml of IPA then disconnect
5	Connect SA3 to LA, inject 10 ml of IPA into infusion set (connected to intravenous bag) then disconnect
6	Connect SA3 to LA, withdraw 5 ml of IPA from infusion set then disconnect

Note. CSTD = closed-system drug-transfer device; SA = syringe adaptor; VA = vial adaptor; IPA = isopropyl alcohol; LA = line adaptor.

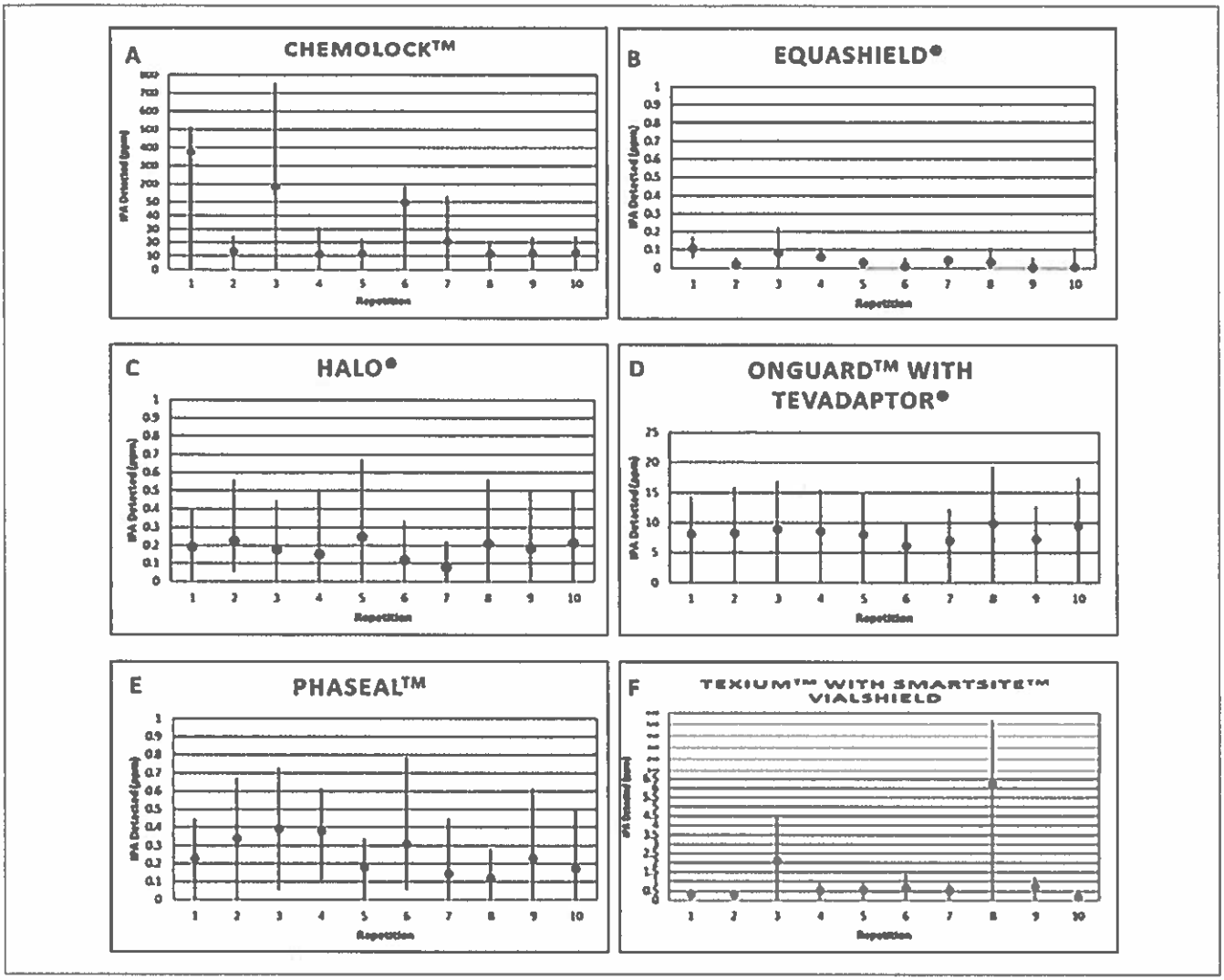

Figure 2. Level of IPA vapor escape detected in ppm throughout 14 steps repeated for 10 repetitions in task 1 for six different CSTDs. (NIOSH performance threshold set at 1.0 ppm).

Note. Data represent the range and mean values. Graph scale = A (0-800), B, C, E (0-1), D (0-25), and F (0-60). Also note the ppm scaling differences between graphs. IPA = 70% isopropyl alcohol; CSTD = closed-system drug-transfer device; NIOSH = National Institute for Occupational Safety and Health.

Study Measurements and Statistics

Before the start of task 1 and task 2 plus added steps, the background concentrations (BG) of IPA vapor inside the test chamber were measured within the first 5 seconds of starting each test run (should be less than or equal to LOD [0.3 ppm]). As recommended in the NIOSH protocol, each reported value was adjusted by subtracting the BG value from each measured value. The readings were normalized by multiplying every adjusted value by 0.56 based on having 56% of the chamber volume. Normalized values were corrected by eliminating any negative or zero values and reporting them as zero IPA detected to produce the zero-corrected value (BG-0) for each step in each task. The maximum of the BG-0 values (BG-0max) and the mean (average BG-0) were then calculated for every 10 repetitions for each task. Thus, each CSTD task resulted in 10 BG-0max values (one per repetition) and 10 average BG-0 values. Following these steps, the mean was calculated for each set of the 10 BG-0max values and each set of the 10 average BG-0s. Those mean values (mean of BG-0max, mean of average BG-0) represented the quantifiable performance of the CSTD devices matched to the 1 ppm NIOSH performance threshold for successful containment.

Results

There were 20 repetitions completed for each of the six CSTD models, with 10 repetitions done per each task. The results for IPA levels detected in task 1 for the six tested CSTDs are presented in Figure 2. Average BG-0 IPA detected values for three

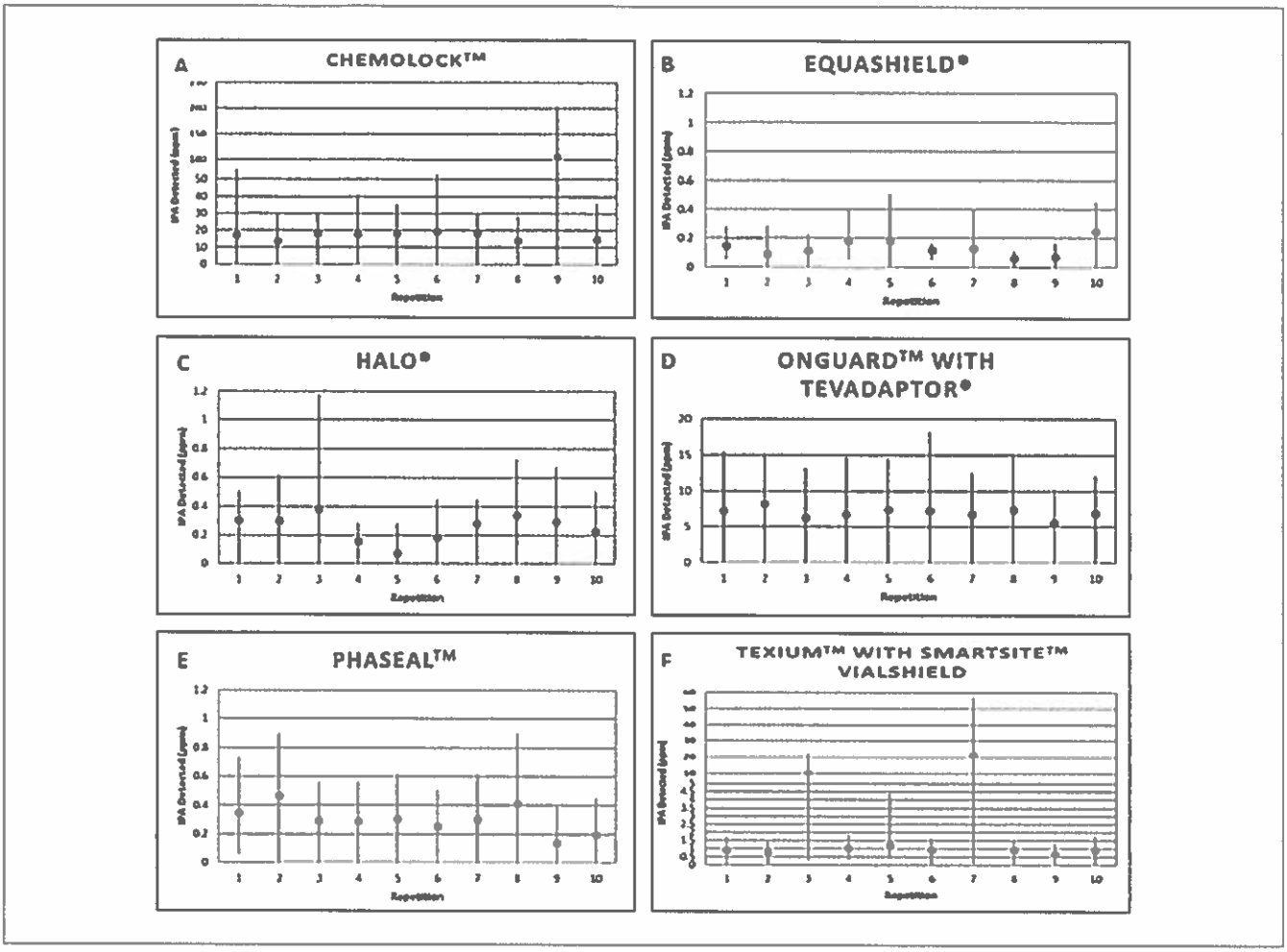

Figure 3. Level of IPA vapor escape detected in ppm throughout 16 steps in task 2 followed by six added steps repeated for 10 repetitions for six different CSTDs. (NIOSH performance threshold set at 1.0 ppm.)
Note. Data represent the range and mean values. Graph scale = A (0-250), B, C, E (0-1.2), D (0-20), and F (0-60). Also note the ppm scaling differences between graphs. IPA= 70% isopropyl alcohol; CSTD = closed-system drug-transfer device; NIOSH = National Institute for Occupational Safety and Health.

devices: Equashield®, HALO®, and PhaSeal™ all fell below the 1.0 ppm quantifiable performance threshold for successful containment per the NIOSH draft protocol while the remaining three CSTDs (ChemoLock™, OnGuard™ with Tevadaptor®, and Texium™ with SmartSite™ VialShield) showed average BG-0 IPA detected levels greater than 1.0 ppm (please note the ppm scaling differences on the individual device graphs). The same results were observed for task 2 plus the added steps (Figure 3). For task 2 results without the added steps, please refer to supplemental material provided electronically. Consequentially, means of average BG-0 and means of BG-0max values (as seen in Table 5) for Equashield®, HALO®, and PhaSeal™ were less than 1.0 ppm for task 1 and task 2 plus the added steps. On the contrary, ChemoLock™, OnGuard™ with Tevadaptor®, and Texium™ with SmartSite™ VialShield means of average BG-0 and means of BG-0max were above 1.0 ppm throughout the IPA manipulation process.

Based on the performance threshold set by NIOSH, only three of the six tested CSTD brands successfully contained IPA: Equashield®, HALO®, and PhaSeal™.

Discussion

In 2015, NIOSH developed a draft protocol to establish testing standards for CSTDs to determine their effectiveness in containing liquid, aerosol, and vapor states of medications during preparation, compounding, and administration processes.[39] The purpose of this study was to test six currently available CSTDs using a modified 2015 NIOSH vapor containment performance draft protocol. In this study, three of the six tested CSTDs (Equashield®, HALO®, and PhaSeal™) performed as truly closed systems measured by IPA release using the Miran SapphIRe analyzer during compounding and administration tasks. While this study utilized the same steps in tasks 1 and 2

Table 5. Means for Both (BG-0max) and (Average BG-0) Values for Each CSTD Task in Parts Per Million.

	Task 1		Task 2 + added steps	
CSTD device (n = 10)	Mean BG-0_{MAX}	Mean of average BG-0	Mean BG-0_{MAX}	Mean of average BG-0
ChemoLock™	173	71.14	55.49	25.81
Equashield®	0.101	0.042	0.297	0.135
HALO®	0.47	0.182	0.566	0.255
OnGuard™ with Tevadaptor®	14.9	8.226	14.13	7.011
PhaSeal™	0.543	0.252	0.622	0.25
Texium™ with SmartSite™ VialShield	6.524	1.234	9.43	3.942

Note. BG = background; CSTD = closed-system drug-transfer device; n = number of repetitions.

as the published draft protocol, modifications were made to the process in task 2 to further challenge the devices. Adding steps to task 2 simulates real-world clinical practice for HD compounding and administration when multiple vial accesses and drug transfers are involved. Furthermore, it confirms the claims of CSTD manufacturers that connectors are effective even after being subjected to an extreme number of connections. This is especially important in protecting the health care worker and assuring a high level of safety from HD exposure. Also, 10 repetitions were used for each task instead of four as specified in the NIOSH protocol to assure that the worker has developed familiarities with the device. With only four repetitions, allowances for outliers are minimal. In addition, it more closely represents the real-world daily repetition of drug preparation.[34] The task manipulations were conducted in a glove chamber smaller than the one used at NIOSH. Since ppm of IPA/air was measured, the smaller volume in the test should have yielded higher concentrations of IPA as compared to prior studies.[40] The LOQ is the concentration at which analytes can be definitively quantified, and it was assigned as the pass/fail performance threshold.[39] Study results showed that Equashield®, HALO®, and PhaSeal™ had significantly lower mean BG-0max and mean of average BG-0 throughout the sequential tasks (<1.0 ppm) when subjected to multiple manipulations of the devices (Table 5). Regardless of whether the additional steps were included in task 2 (see S1 Figure and S1 Table in the supplemental material), Equashield®, HALO®, and PhaSeal™ components consistently contained IPA vapor. Alternately, ChemoLock™, OnGuard™ with Tevadaptor®, and Texium™ with SmartSite™ VialShield did not meet the quantifiable performance threshold. These findings are to a degree consistent with the results of a previous study by Forshay et al[40] that compared six devices using the 2015 NIOSH draft protocol measuring vapor levels after each of 10 steps for each of the four repetitions. We tested all the same devices except the ChemoClave®, which we exchanged for HALO®. In addition, our study differed in that we added manipulations to task 2 and measured vapor levels after each of 36 steps for each of the 10 repetitions.

Currently, two CSTD technologies are on the market, physical barrier and air-cleaning technology. The 2015 NIOSH protocol is only applicable for the physical-barrier CSTDs and not intended for CSTDs designed to operate using air-cleaning or filtration technologies.[39] The vapor pressure of IPA is much higher than any HD currently marketed which may affect the integrity of these air-cleaning systems and lead to positive results. This concern has been noticed in the Forshay et al[40] study that compared both technologies against the NIOSH protocol. In our study, the two technologies of CSTDs were tested using NIOSH protocol to compare how commercially available CSTDs were able to contain IPA vapor. However, the effect of IPA's high vapor pressure on air-cleaning or filtration technologies CSTDs needs to be taken into consideration when evaluating the results. Also, this was an attempt to understand why air-cleaning systems were excluded from the 2015 vapor protocol as these devices are already on the market along with physical-barrier systems, and alcohol is already contained in several HDs. Some of the physical-barrier CSTDs have already adopted changes in their vial adaptors such as ChemoLock™ and Texium™ with SmartSite™ VialShield. These adaptations allow these CSTDs to function without needles in their vial adaptors, in contrast to other physical barriers. Consequently, changes in existing device systems have blurred the differences between air-cleaning technology and physical-barrier technology; this study attempted to examine the performance of several of the changed systems as well.

Limitations of the NIOSH's 2015 draft protocol (eg, being applicable only for physical-barrier CSTDs and using IPA as a challenge agent) were addressed in a new draft universal performance test protocol that was published in 2016. The new 2016 draft protocol included CSTDs that use air-cleaning technology and nine potential surrogate compounds for use as challenge agents applicable to all types of CSTDs. NIOSH stated that the vapor pressure of the proposed surrogate is more representative of the HDs compared to IPA, which can affect the integrity of the air-cleaning CSTDs.[41] In a recently published study, Wilkinson et al[42] evaluated four CSTDs against the new proposed NIOSH performance protocol and found that 2-phenoxyethanol is an ideal drug surrogate for CSTD testing. However, this 2016 NIOSH protocol is still in review. Consequently, the 2015 NIOSH

draft protocol is still an appropriate evaluation tool in some situations. Currently, with no published final universal performance standard for evaluating CSTD containment, there is still no accepted quantitative process to distinguish between available products.

Conclusion

Equashield®, HALO®, and PhaSeal™ components tested in this evaluation met the quantifiable performance threshold set by the 2015 NIOSH Draft Vapor Containment Performance Protocol for CSTDs while ChemoLock™, OnGuard™ with Tevadaptor®, and Texium™ with SmartSite™ VialShield tested components did not. Those handling HDs should include quantitative containment performance as part of their selection criteria for protective equipment.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material is available in the online version of the article.

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