Drugs & Therapy Perspectives (2022) 38:177–184
https://doi.org/10.1007/s40267-022-00905-x

ORIGINAL RESEARCH ARTICLE

Evaluation of three barrier-type closed system transfer devices using the 2015 NIOSH vapor containment performance draft protocol

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Accepted: 22 February 2022 / Published online: 16 March 2022

Abstract

Background Closed System Transfer Devices (CSTD) have been developed to reduce healthcare worker exposure to hazardous drugs during medication handling. To evaluate CSTD performance in preventing the escape of drug vapors, the National Institute for Occupational Safety and Health (NIOSH) developed a 2015 draft testing protocol incorporating two compounding tasks utilizing 70% isopropyl alcohol (IPA) as a medication surrogate.

Purpose The objective of this study was to evaluate the performance of three CSTDs (Chemolock [ICU Medical Inc., San Clemente, CA], PhaSeal [BD, Franklin Lakes, NJ], and Equashield [Equashield, Port Washington, NY]) in preventing the escape of drug vapor in accordance with the 2015 NIOSH draft protocol during simulated compounding and administration tasks.

Methods The protocol was modified for the CSTDs to be used in accordance with manufacturer instructions for use and to represent clinical practice through repeated CSTD connections. Tasks were executed with each of the three CSTDs using 70% IPA as the medication surrogate to simulate compounding of a lyophilized drug, intravenous (IV) bag preparation (task 1), and bolus administration through an IV set (task 2). A positive control was performed by completing both tasks in duplicate, utilizing a needle and syringe instead of the CSTD to simulate preparation and injection through luer connectors. Differences in time to complete each simulated task was also evaluated.

Results The three CSTDs had statistically equivalent performance and maintained IPA vapor levels below the limit of detection (LOD) of 1.0 ppm. Positive controls had mean vapor release of 17.40 ppm and 23.45 ppm for tasks 1 and 2, respectively. Positive controls also required statistically longer mean time to complete both tasks, followed in decreasing order by PhaSeal, Equashield, and Chemolock.

Conclusions This study suggests that when evaluated in accordance with the 2015 NIOSH draft protocol, the three CSTDs are equivalent in their ability to prevent IPA vapor release while differences in time required for task completion may exist.

Introduction

Healthcare worker exposure to antineoplastic drugs affects both cancerous and noncancerous cells, resulting in side effects such as: skin rashes, infertility, miscarriage, birth defects, and possibly leukemia and other cancers [1–9]. The National Institute for Occupational Safety and Health (NIOSH) and the United States Pharmacopeia (USP) have developed guidelines describing the pharmacy requirements for the handling and preparation of hazardous preparations to protect healthcare workers from these adverse effects [2, 10–14]. These standards encompass the facilities and equipment, personnel training, policies and procedures, product and preparation requirements, and quality assurance processes [2, 14]. Central to provider safety are the mandates for primary engineering controls and personal protective equipment to be used in accordance with administrative controls.

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Key Points

The Closed System Transfer Devices (CSTDs) evaluated all demonstrated similar ability to restrict 70% isopropyl alcohol (IPA) vapor to below the IPA analyzer limit of quantification during simulated compounding and administration tasks.

Design differences between the CSTDs tested may account for workflow and time savings differences and should be evaluated when choosing a CSTD for use.

Surrogate vapor measurements should be correlated to hazardous drug vapor measurements for defining performance thresholds that are more clinically meaningful and instrument independent.

Closed System Transfer Devices (CSTDs) have been shown to decrease drug contamination within the clinical environment, which may reduce a healthcare worker's exposure to antineoplastic drugs [15–19]. This evidence has led to the recommendation within USP General Chapter <800> to consider using CSTDs to transfer hazardous drugs from primary packaging (such as vials) to dosing equipment (such as infusion bags, bottles, or pumps) [14]. A CSTD is defined by NIOSH as a drug transfer device that mechanically prevents the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system. This definition has been adopted within USP General Chapter <800>, which considers a CSTD to be a supplemental engineering control that offers additional levels of protection during compounding and administration [12, 14]. CSTDs are broadly classified into two design types: physical barrier and air filtration.

Although USP General Chapter < 800 > recommends the use of a CSTD for compounding and requires a CSTD for the administration of hazardous drugs, when possible, the criteria for evaluating the performance of the CSTD has not yet been established [14]. The characteristics of CSTD performance are instead described through independent, peer-reviewed studies and commercial performance claims based on manufacturer's internal data. These sources of information describing device performance are often used in conjunction with factors such as cost and potential resource time savings to inform purchasing decisions.

To provide guidance for evaluating the performance of barrier-type CSTDs in maintaining a closed system and preventing the escape of vapor contamination, a testing protocol called "A Vapor Containment Performance Protocol for Closed System Transfer Devices Used During Pharmacy Compounding and Administration of Hazardous Drugs" was made available by NIOSH in 2015, which remains in draft form [12]. The protocol utilizes 70% isopropyl alcohol (IPA) as the surrogate medication during simulated compounding tasks and is only applicable to barrier-type CSTDs, therefore excluding the evaluation of filtration type devices.

The primary objective of this study was to evaluate the performance of three barrier-type CSTDs in preventing the transfer of 70% IPA vapor into the surrounding environment during simulated compounding tasks. Time to complete each simulated compounding task was assessed as a secondary outcome for each device.

Methods

Three CSTDs (Chemolock [ICU Medical Inc., San Clemente, CA], PhaSeal [BD, Franklin Lakes, NJ], and Equashield [Equashield, Port Washington, NY]) were evaluated in accordance with the 2015 NIOSH draft protocol (CDC-2015-0075-003) [12] with modifications for the CSTDs to be used in accordance with manufacturer instructions and better represent clinical practice. The NIOSH draft protocol utilizes 70% IPA as a hazardous drug surrogate to simulate two compounding tasks: first (task 1), the compounding of a lyophilized drug and intravenous (IV) bag preparation, and second, (task 2) the compounding of a lyophilized drug and bolus administration.

The study testing was performed during May 2020 at the ICU Medical, Inc, analytical laboratory (San Clemente, CA, USA). Due to COVID-19 facility personnel access limitations, the protocol was performed by an ICU Medical technician trained on the usage of the CSTD systems utilizing the current instructions for use and publicly available training videos. Experimental data collection and a video record of the study performance was retained for documentation of proper CSTD use technique and adherence to the study protocol.

The tasks were performed within an environmental test chamber comprised of a Secador Techni-dome 360 Vacuum Desiccator with custom 12-inch extension ring and modification as described per the NIOSH draft protocol [12]. IPA vapor concentration was analyzed using a Thermo Scientific Miran SapphIRe Infrared Analyzer model 205B-XL, hereafter referred to as IPA analyzer. The IPA analyzer was operated using the long path length with wavelength 8.852 nm in IPA-L detection mode. Data was logged once every second and recorded in parts per million (ppm). A span check and calibration were performed with nitrous oxide and sulfur hexaflouride gases to confirm that operation of the IPA analyzer was within normal parameters.

Prior to performing each task, the environmental chamber was purged using compressed air to clean any residual IPA vapor and the IPA analyzer zeroed using the provided

charcoal filter to ensure a consistent background reading (BG_0). Background levels within the chamber were then monitored for 5 s prior to initiating testing. If the background level within the chamber was determined to be greater than the limit of detection (LOD) of 0.3 ppm IPA, the chamber was opened, purged again and the test components inspected for potential leaks. Logging was initiated and the task performed, after the background level was determined acceptable. Maintaining a low background level for each task replicate is intentional to avoid larger background corrections allowed within the NIOSH draft protocol for levels exceeding the IPA analyzer LOD. If higher vapor concentrations are present at the task initiation, a negative offset to the reading can potentially be created if the vapor dissipates within the chamber faster than release from the device, artificially lowering the vapor amount detected by the IPA analyzer. Background levels for each task were instead monitored and only minor background corrections performed to zero out the IPA analyzer noise and provide a consistent zero for task vapor measurements.

Task 1 simulated the reconstitution of a lyophilized drug vial followed by two transfers of 45 mL each into an IV bag. Materials for task 1 were prepared in accordance with the NIOSH draft protocol; two 100 mL vials each filled with 50 mL of IPA were placed into the chamber along with a 60 mL syringe, 500 mL IV bag and CSTD for each evaluation of task 1. Background levels were first confirmed to be below the IPA analyzer LOD, then both vials were then spiked with a CSTD vial spike. A 60 mL syringe with CSTD connector was then used to remove 45 mL of IPA from the first vial and transfer the volume to the second vial as simulated reconstitution. Two 45 mL volumes (90 mL total) were then transferred from the second vial to an IV bag accessed through a CSTD bag spike to simulate compounding.

Task 2 simulated the reconstitution of a lyophilized drug followed by two simulated IV bolus administrations. Materials for task 2 were prepared in accordance with the NIOSH draft protocol; Two 100 mL vials each filled with 50 mL of IPA, a syringe, an administration set with y-site, and CSTD for evaluation were placed into the chamber. In addition to these materials specified by the NIOSH draft protocol, an empty 100 mL IV waste bag was also attached at the end of the IV set to capture the infused IPA. This simulates the clinical administration of a bolus dose more closely rather than delivering the bolus up the IV set into to the IV bag. Background levels were then confirmed before spiking both vials with a CSTD vial spike. A 60 mL syringe with CSTD connector was then used to transfer 45 mL of IPA from the first vial to the second vial. Two 45 mL volumes were then injected into the IV set y-site through a CSTD y-site adapter to simulate patient administration. IPA vapor concentration was logged at 1 s intervals throughout each task.

Modifications to the NIOSH 2015 protocol were implemented to use CSTDs in accordance with manufacturer instructions to represent current clinical practice more effectively. These modifications to the NIOSH draft protocol would not foreseeably impact results in either task. In task 1, the CSTD bag spike was connected to the sterile saline-only bag outside of the environmental chamber due to the limitations of conducting such manipulations inside the chamber. For the same reason, in task 2 the standard administration set was connected to the saline-only IV bag and primed with saline outside the environmental chamber. As the IV bag in both tasks contains only normal saline at the time of connecting the CSTD bag spike or administration set, there is no contribution to the concentration of IPA in the chamber whether assembled inside or outside of the enclosure. Specifically for task 2, an empty 100 ml waste IV bag was also assembled to the distal luer of the administration set outside of the environmental chamber. The waste bag was added to collect injected surrogate and prevent over pressurizing the administration set and IV bag, which would not happen in clinical use.

While the NIOSH draft protocol included 30 s pauses at specific intervals throughout the testing, the method in this study excludes pauses which may not be included in compounding and administration practice. In lieu of the 30 s stop times between steps, additional readings were taken throughout each task to evaluate the CSTD containment performance at sub-divided intervals. The additional readings allowed for a more robust data collection model and accounted for the entire task process. In addition, only one syringe and CSTD adaptor was employed for task 1 to transfer the sequential 45 mL volumes of IPA from the vial to the IV Bag, which is a more likely clinical occurrence and worst-case simulation. These modifications properly aligned the CSTDs with both their instructions for use, as well as the actual clinical workflow that these systems are subjected to.

Each task was performed 6 times for each of the three CSTD devices. A positive control consisting of an 18 ga needle attached to the syringe, instead of a CSTD, was performed twice for each simulated task. Timestamps for the start of the task, and each reading were recorded by a clock synced with the Miran SapphIRe internal clock to within 1 s prior to start of each task. In total, the procedure generated 20 recordings per task (40 total) and four positive controls.

Several intermediate readings were also evaluated during each task in addition to the single final reading taken at the task completion as instructed within the NIOSH draft protocol [12]. These intermediate readings are defined in Table 1. The additional readings provide the ability to evaluate which subsection of the task that presents the most risk, or potential for vapor release. The different subsections for

the additional readings were defined by the CSTD disconnection steps within the protocol. The maximum value of measured vapor logged, during the task subsection sampling, were used as the representative maximum readings for data analysis.

Maximum vapor concentration and duration measurements were calculated from logged data recorded from the device and synced by timestamp. In accordance with the NIOSH draft protocol, the background reading (BG_0) was taken as the mean over the first 5 s prior to initiating the task. No background correction was required, as indicated by the NIOSH draft protocol, as all background measurements were below the IPA analyzer's LOD.

Statistical analysis

Vapor concentration and duration measurements were each analyzed by one-way analysis of variance (ANOVA), with device as a factor, and fit to the maximum background-corrected measurements for task 1, task 2, and duration separately. The vapor measurement data for the two tasks were also pooled and analyzed with a 2-way ANOVA with device and task as factors for the 2-way interaction. A similar 2-way ANOVA was also performed for task duration data.

Residual and individual value plots were used to check the normality and homogeneity of variance assumptions of the models. The mean and variability in the maximum vapor concentrations (ppm) was observed to be small for the devices, however the values were large for the positive control and the data did not display homogeneity of variance, a required assumption when analyzing these data by ANOVA. To achieve homogeneity of variance for statistical analysis, vapor measurement data were transformed using a generalized weighted linear model prior to statistical analysis. Duration times demonstrated homogeneity of variance and were not transformed for analysis. All models were fit using Minitab v19.

Table 1 Description of additional task readings

Reading	Task 1	Task 2
BG_0	Background Reading	Background Reading
1	Attach Vial Spikes	Attach Vial Spikes
2	Fill Transfer Syringe	Fill Transfer Syringe
3	Fill Dose Syringe 1	Fill Bolus Syringe 1
4	IV Bag Transfer 1	Fill Bolus Syringe 2
5	Fill Dose Syringe 2	Y-site Push 1
6	IV Bag Transfer 2	Y-site Push 2

Results

Maximum vapor concentration by device and task is presented in Fig. 1. The vapor measurement data for task 1 and task 2 are available within supplementary Tables S1 and S2, respectively. All three CSTDs exhibited maximum readings of 70% IPA vapor below the 1.0 ppm limit of quantification of the IPA analyzer during the simulated tasks. In contrast, the needle and syringe positive control, resulted in 70% IPA vapor measurements that were higher than the devices tested, exceeding the IPA analyzer's lower limit of quantification.

Figure 2 presents the average time to complete each task by device. Duration to complete the tasks was statistically determined to be significantly longer for the positive control in each of tasks 1 and 2, as compared to the three device types and use of all three devices resulted in a significant decrease in duration in each task ($p \leq 0.001$). When pooling both tasks together, all CSTDs demonstrated significantly different durations ($p \leq 0.001$). Ranked in order of means, ChemoLock being the fastest (2.66 mins), followed by Equashield (3.36 mins), Phaseal (4.48 mins) and then the positive control (5.85 mins) ($p \leq 0.001$).

Table 2 reports the maximum IPA vapor measurement for each task along with task duration. Table 3 reports the mean, standard deviation, and confidence interval of the vapor concentration and task duration of each task. The positive control exhibited the highest level of IPA vapor, on average, in task 1 (17.4 ppm) and task 2 (23.5 ppm). The three devices demonstrated statistically less vapor detected than the positive control only in task 2 ($p = 0.001$), but not in task 1 ($p \geq 0.134$). This distinction is attributed to the much larger variance observed in the task 1 positive control.

When pooling data for task 1 and 2 to increase sample size, and reduce variance, all devices exhibited significantly less vapor concentration detected, on average, than the pooled positive controls ($p < 0.0005$). Measurements from the three devices were determined to have statistically equivalent IPA vapor release below the IPA 1.0 ppm limit of detection when pooled across tasks 1 and 2. It could be extrapolated from this pooled analysis that the positive control would become statistically different from the three devices given a higher sample size.

Discussion

The purpose of this study was to evaluate the environmental release of IPA vapor with use of three physical barrier CSTDs during simulated compounding and administration tasks defined within the 2015 NIOSH draft protocol with modifications for better clinical alignment. All three of the

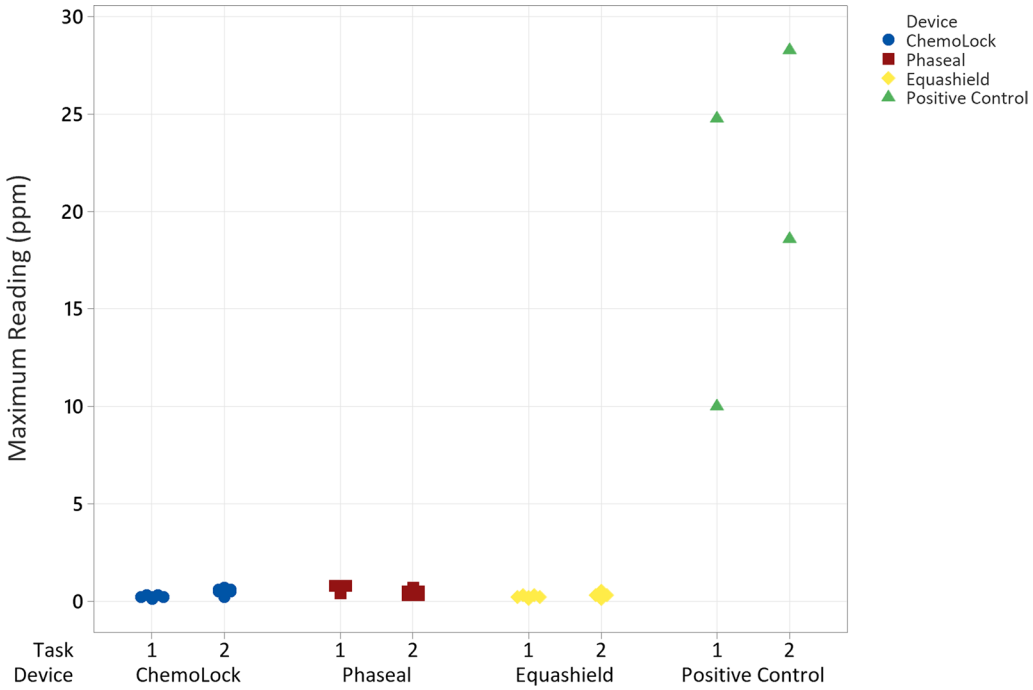

Fig. 1 Plot of maximum vapor detected during each task per device.

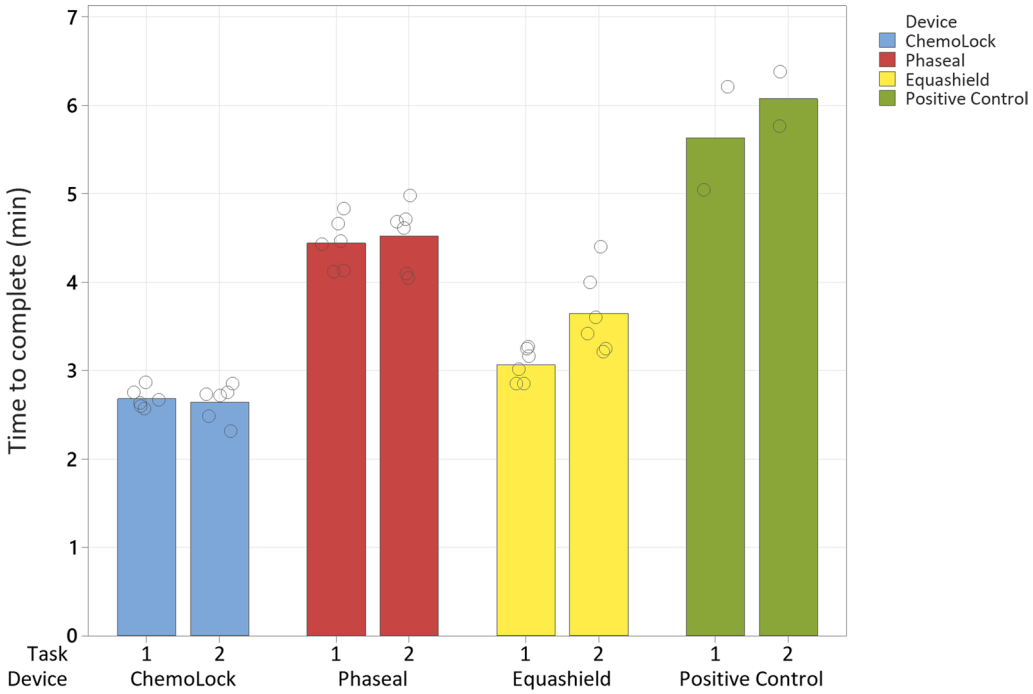

Fig. 2 Plot of total time to complete Task 1 and Task 2 for each sample.

tested CSTDs contained IPA vapor below the 1.0 ppm limit of quantification and demonstrated statistically equivalent IPA vapor release, similar to results within previous publications [20, 21].

The results from this study provide an additional perspective to work performed by Halloush, et al. [21], where testing was performed within a reduced chamber volume, and a normalizing factor applied to adjust for the different

Table 2 Maximum zero-adjusted IPA vapor measurement data for tasks 1 and 2 in parts per million (ppm) and task duration for both tasks in minutes.

CSTD device	Sample	Task 1		Task 2	
		Maximum reading (ppm)	Duration (min)	Maximum reading (ppm)	Duration (min)
ChemoLock	1	0.2	2.87	0.2	2.85
	2	0.2	2.67	0.6	2.73
	3	0.1	2.63	0.5	2.32
	4	0.2	2.75	0.5	2.48
	5	0.3	2.57	0.7	2.75
	6	0.3	2.60	0.6	2.72
Phaseal	1	0.4	4.13	0.3	4.10
	2	0.6	4.43	0.7	4.05
	3	0.8	4.67	0.3	4.98
	4	0.5	4.47	0.4	4.62
	5	0.8	4.12	0.5	4.68
	6	0.7	4.83	0.5	4.72
Equashield	1	0.2	3.25	0.3	3.42
	2	0.1	2.85	0.5	3.25
	3	0.3	3.02	0.2	4.40
	4	0.3	3.17	0.3	3.22
	5	0.2	2.85	0.1	3.60
	6	0.2	3.27	0.4	4.00
Positive control 1		24.8	6.22	28.3	6.38
Positive control 2		10.0	5.05	18.6	5.77

Table 3 Vapor concentration summary statistics for tasks 1 and 2 in ppm

Device	*N*	Task 1			Task 2		
		Mean	SD	95% CI	Mean	SD	95% CI
Vapor (ppm)							
Positive control	2	17.40	10.47	(– 76.63, 111.43)	23.45	6.86	(– 38.18, 85.08)
ChemoLock	6	0.22	0.08	(0.14, 0.30)	0.52	0.17	(0.34, 0.70)
PhaSeal	6	0.63	0.16	(0.46, 0.81)	0.45	0.15	(0.29, 0.61)
Equashield	6	0.22	0.08	(0.14, 0.30)	0.30	0.14	(0.15, 0.45)
Duration (min)							
Positive control	2	5.63	0.83	(5.20, 6.07)	6.08	0.47	(4.21, 4.84)
ChemoLock	6	2.68	0.11	(2.43, 2.93)	2.64	0.20	(2.32, 2.96)
PhaSeal	6	4.44	0.28	(4.19, 4.69)	4.53	0.37	(5.52, 6.63)
Equashield	6	3.07	0.19	(2.82, 3.32)	3.65	0.47	(3.33, 3.97)

volume specified within the protocol. This test repeats some of the previous work performed [20, 21], with additional modifications for greater clinical alignment while also utilizing the full chamber volume specified for testing. Not all CSTD systems were able to be included in the study and the two vented systems were intentionally excluded. The NIOSH 2015 draft protocol indicates 70% IPA as the surrogate and applicable to only physical barrier CSTDs, and not to filtration CSTD systems [12]. For this reason, the ICU Medical ChemoLock™ vented system was replaced by the ChemoLock™ physical barrier (non-vented) system for evaluation.

This work similarly expands prior work performed by Forshay, et al. [20] through evaluating the devices with modifications for clinical alignment. The tasks of this evaluation were chosen to be sub-divided in a different manner, focusing specifically on actions where the CSTD systems were disconnected as this was hypothesized to be the most

likely action for releasing vapor. Time to complete each task was also measured as an additional factor to consider when evaluating a CSTD.

The time to complete a task with each CSTD demonstrated statistically significant differences. As all actions were kept the same for each device, the completion time differences are likely attributed to differences in design that may affect the number and complexity of required steps to complete the actions required within each task. Use mechanisms which engage through an in-line push mechanism without orientation and rotation requirements differ from those which require orientation, twist, and push. These design differences likely contribute to the time it takes for a technician to successfully connect or disconnect the system components. Differences in fluid path geometry across CSTDs also impacts resistance to flow while transferring fluids. For similar effort from the technician, a device with greater flow resistance would take longer to transfer the same amount of fluid. If tasks were more complex or inherently longer, this could impact time to completion by creating a lower ceiling on efficiency improvements. Further work is needed to determine specific causes for the longer time taken to complete tasks.

Extrapolation of the results of this study to CSTD performance in the handling of hazardous medications may also require additional analysis. IPA vapor concentration measurements observed are useful as a comparative index for CSTD containment but have yet to be correlated with the reduction in hazardous drugs expected to occur during actual pharmacy compounding or drug administration manipulations. Studies evaluating the containment performance of CSTDs, including this work, have relied on the measurement instrument's limit of quantification for a performance threshold [20, 21]. This is a short-term solution, as different instruments or future detection methods will have varying limits of quantification. Non-detection is a must for hazardous drugs; however the same criteria should not be conflated with performance thresholds for specific surrogates which are much more volatile by design. IPA has a higher vapor pressure many orders of magnitude higher than hazardous drugs currently used, which may result in higher detection levels than would be experienced with current hazardous drugs. For example, at 25 °C, the vapor pressure of IPA is approximately 45 mmHg, whereas a common hazardous drug with high vapor pressure is thiotepa, with a vapor pressure of 0.0094 mmHg [22].

Additional research that includes more clinically relevant surrogates as well as verification of the existence and concentration of hazardous vapor for commonly compounded and administered drugs may provide useful data to support correlated exposure limits. It is expected that the surrogate performance threshold would eventually be correlated with vapor measurements of commonly used hazardous drugs to define clinically relevant performance thresholds, that no longer relies on specific detection instruments.

Conclusion

These study results show that the three barrier-type CSTDs were effective in preventing the escape of IPA in vapor form. The three brands of CSTDs all fell below the 1.0 ppm limit of quantification and were determined to be statistically equivalent in performance. Given similar containment, other factors of CSTDs should be considered, such as bonded, locking mechanism, and potential time savings, which can also impact safety and workflow when using a CSTD. The comparative evaluation of the duration required to complete the simulated tasks indicated that all three evaluated CSTDs took less mean time to complete the simulated tasks than the positive control. Among the CSTDs, the fastest was the ChemoLock, followed by the Equashield, and the PhaSeal being the slowest of the CSTDs evaluated.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40267-022-00905-x.

Acknowledgements Statistical analysis was performed and provided by Al Parker of Montana State University College of Engineering Center for BioFilm Engineering, a National Science Foundation Engineering Research Center.

Declarations

Competing interests and funding AS and SH were both compensated by ICU Medical, commensurate to the time devoted to the review of data and development of manuscript.

Conflicts of interest AS and SH report no conflicts of interest.

Availability of data and material Data are available on request from the authors.

Code availability Data are available on request from the authors.

Author contributions AS and SH contributed equally to the development of the manuscript.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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