Multicenter evaluation of a new closed system drug-transfer device in reducing surface contamination by antineoplastic hazardous drugs

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Purpose. Results of a study to evaluate the effectiveness of a recently introduced closed-system drug transfer device (CSTD) in reducing surface contamination during compounding and simulated administration of antineoplastic hazardous drugs (AHDs) are reported.

Methods. Wipe samples were collected from 6 predetermined surfaces in compounding and infusion areas of 13 U.S. cancer centers to establish preexisting levels of surface contamination by 2 marker AHDs (cyclophosphamide and fluorouracil). Stainless steel templates were placed over the 6 previously sampled surfaces, and the marker drugs were compounded and infused per a specific protocol using all components of the CSTD. Wipe samples were collected from the templates after completion of tasks and analyzed for both marker AHDs.

Results. Aggregated results of wipe sampling to detect preexisting contamination at the 13 study sites showed that overall, 66.7% of samples (104 of 156) had detectable levels of at least 1 marker AHD; subsequent testing after CSTD use per protocol found a sample contamination rate of 5.8% (9 of 156 samples). In the administration areas alone, the rate of preexisting contamination was 78% (61 of 78 samples); with use of the CSTD protocol, the contamination rate was 2.6%. Twenty-six participants rated the CSTD for ease of use, with 100% indicating that they were satisfied or extremely satisfied.

Conclusion. A study involving a rigorous protocol and 13 cancer centers across the United States demonstrated that the CSTD reduced surface contamination by cyclophosphamide and fluorouracil during compounding and simulated administration. Participants reported that the CSTD was easy to use.

Keywords: antineoplastic drugs, closed system drug-transfer device, CSTD, cyclophosphamide, hazardous drugs, surface contamination, wipe sampling

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Worker exposure to antineoplastic hazardous drugs (AHDs) during the course of providing care to patients has been a concern for several decades due to the potent and toxic nature of the drugs used and their nonselectivity.[1,2] These drugs attack cancer cells and healthy cells alike and, once absorbed into the body, make no distinction between patients and workers. Many of the AHDs are mutagenic, carcinogenic, and reproductive toxins, exposing healthcare workers to the risk of immediate effects such as skin reactions and long-term effects including poor reproductive outcomes and an increased incidence of cancer.[1]

Dermal contact with AHD-contaminated surfaces is believed to be the primary cause of AHD absorption in healthcare workers.[3,4] Demonstrat-

ed sources of AHD surface contamination include residue on the outside of drug vials, fugitive drug escaping during the compounding of AHD doses, and leaks and mishaps during administration of these doses to patients, all of which can result in surface contamination throughout the work environment.[5,6] Recent studies indicate that more workers than previously thought are at risk for exposure.[7,8] Detectable urine levels of the marker AHD cyclophosphamide have been documented in workers present in oncology patient care areas but not directly involved in drug preparation or administration, including patient care assistants, oncologists, and clinical pharmacists.[8]

Reduction of overall AHD surface contamination should reduce worker uptake of drug and subsequently reduce the risk of harm. A device was developed in Sweden in the mid-1990s to improve the handling of AHDs during the compounding and administration processes.[9] This type of device is now known as a closed system drug-transfer device (CSTD), an apparatus defined by the U.S. National Institute for Occupational Safety and Health (NIOSH) in 2004 as 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.[1] The initialism CSTD later came into use, but depending on the source, the definition often does not include the word *drug*, an omission that frequently results in misunderstandings. When tested in peer-reviewed studies, the initially developed device, now called the PhaSeal system (BD, Franklin Lakes, NJ), was successful in providing a reduction in overall AHD surface contamination[9-12] and the presence of drugs in urine samples of healthcare workers.[11] A small study of another CSTD, the Equashield device (Equashield LLC, Port Washington, NY), demonstrated reduced contamination on surfaces not directly adja-

KEY POINTS

- Ongoing surface contamination with antineoplastic hazardous drugs (AHDs) presents a risk to workers who are inadvertently exposed to these drugs, including workers who are not involved with compounding or administration.

- Closed system drug-transfer devices (CSTDs) should reduce AHD leaks and spills during compounding and administration, thereby reducing overall surface contamination in work areas.

- Published peer-reviewed studies of individual CSTDs are needed to adequately evaluate the effectiveness of these devices in reducing surface contamination.

cent to areas used for compounding and administration tasks.[13]

While many researchers have studied the effectiveness of CSTDs, most of the studies have been done with the PhaSeal device, and approaches to testing have varied significantly.[14] There is no generally accepted surrogate for AHDs. Studies using actual drugs as markers are the most useful for determining CSTD containment, with studies involving cyclophosphamide and fluorouracil reported most often in the literature.[14] Even when using AHD marker drugs, there has been no consistent method to quantify the efficacy of the device.

Most of the studies done in actual compounding or patient care areas are "snapshot" studies involving wipe sampling at a single point in time or at a few arbitrary time periods regardless of workload fluctuation[11,15,16]; the researchers did not report the amount of marker drug handled or the type of doses compounded. In other studies,

such as the study of Zock et al.,[17] investigators have used CSTDs to transfer 5-mL increments of AHDs to simulate compounding, whereas in clinical practice the transfer of larger volumes of AHDs in large syringes is more likely. Additionally, the authors of published studies generally did not report which components of the CSTD were used, implying that all components of a CSTD contribute to an improvement, which may not be the case.[8]

No study has focused specifically on the administration tasks that may result in spills and leaks at the site of infusion delivery to the patient. There has also been little consistency in the sampling sites selected in patient infusion areas, with remote sites (e.g., counters, waste containers) being sampled rather than sites that would most likely be contaminated from a spill during drug administration (e.g., the floor beneath the i.v. pole).[5,11]

The study described in this article was the first to employ a strict protocol for both compounding and administering AHDs that provided for reliability of results across multiple sites. The purpose of the study was to evaluate the performance of a new CSTD in reducing surface contamination during compounding and administering marker AHDs, as measured by wipe sampling. The protocol was reviewed by oncology pharmacists and clinical nurse specialists in oncology for its applicability in evaluating a novel CSTD in cancer center compounding and administration of AHDs. The specific study protocol was submitted to the National Cancer Institute (NCI), a division of the National Institutes of Health (NIH), and after a rigorous peer review of the proposed scientific approach, NCI and NIH grant funding for the study was provided.

Methods

Participant site selection. Study sites were recruited from among NCI-designated cancer centers (www.cancer.gov/research/nci-role/cancer-centers) and the members of the Association of Community Cancer Cen-

ters (www.accc-cancer.org/) located throughout the United States. Nineteen U.S. cancer treatment centers were initially targeted to participate in the study. Table 1 describes the characteristics of the 13 centers ultimately included in the study and notes the reasons for exclusion of the other 6 centers. The sites varied from inpatient settings to ambulatory care infusion settings. The study criteria required that all sites use class II biological safety cabinets (BSCs) to compound AHDs, but venting characteristics of the BSCs and compounding areas were not stipulated. As in a prominent study of 3 university-based U.S. cancer centers,[5] pharmacy designs varied at the different study sites, ranging from basic rooms to cleanrooms with anterooms. Meeting *U.S. Pharmacopeia* (*USP*) standards for sterile compounding areas was not stipulated as a study condition. Several of the sites used a CSTD for preparing AHDs prior to the study. Assessing existing site-specific practices (e.g., current use of a CSTD, specific compounding or

cleaning practices) was not a goal of the study; therefore, this information was not collected or evaluated. All sites utilized chairs with armrests in the infusion areas, where AHDs were administered using a variety of infusion pumps. Selection of initial infusion area wipe sampling locations was based on input from each site's principal investigator (PI) as to which chair was used most frequently to treat patients. For CSTD testing, study site personnel selected a treatment area within the infusion area that was set up to simulate an actual chemotherapy infusion; the selected testing sites included an infusion chair with armrests, an i.v. pole with a mounted infusion pump, the designated floor area underneath the i.v. pole, and objects that would be present during administration of chemotherapy to a patient. No study doses were administered to patients. Each site provided, at minimum, a pharmacy technician and an oncology nurse who used the new CSTD for compounding and administration, respectively. In addition,

a study site coordinator or PI, usually a pharmacist, monitored site and staff activities, including technician compounding, during the study period.

The study site participants had been trained in compounding or administering AHDs during the course of their employment and had at least 1 year of experience in handling AHDs. At each site, a pharmacist monitored technician compounding. For study sites that required investigational or institutional review board clearance for participation of site workers, approval was received prior to the study. Study sites received compensation for direct expenses, including staff participation and supplies, and indirect expenses, including facility fees or preestablished grant rates.

Study team. The study team included licensed pharmacists with expertise in compounding AHDs and nurses experienced with handling AHDs to provide training to site staff in using the new CSTD and to monitor and execute the study protocol. Study team pharmacists and nurses assessed

Table 1. Characteristics of U.S. Cancer Treatment Centers That Served as Study Sites[a]

Site No.[b]	Region	Designation	Clinic Type	Approximate No. Doses Prepared Monthly
3	Midwest	Private practice	AIC	1,200–1,500
4	Southeast	Community-based hospital	IPD + AIC	750
6	Midwest	NCI-designated CC	AIC	1,200
8	Midwest	Private practice	AIC	470
9	Northeast	NCI-designated CC	IPD + AIC[c]	1,120
10	Northeast	NCI-designated CC	AIC	10,000
12	Northeast	Community-based hospital	IPD + AIC	400
13	Southwest	Community-based hospital	IPD + AIC	434
14	Midwest	NCI-designated CC	IPD + AIC	6,300
16	Northeast	NCI-designated CC	AIC	7,000–9,000
17	Southwest	Community-based hospital and CC	AIC	400
18	Northeast	Private oncology practice recently purchased by NCI-designated CC	AIC	200–300
19	Northeast	Community-based hospital affiliated with NCI-designated CC	AIC	600–700

[a]IPD = inpatient department, AIC = ambulatory care infusion center, NCI = National Cancer Institute, CC = cancer center.
[b]Six initially included sites were omitted per exclusion criteria, including failure to provide both pharmacy and nursing staff to execute the protocol and precontaminated and/or exploded drug vials unrelated to the study device.
[c]Study performed in AIC only.

study participants to ensure they were experienced in the safe handling of AHDs, had access to and used appropriate personal protective equipment, understood spill management procedures, had spill kits available, and had appropriate AHD disposal containers and procedures in place. The study team used a fluorescein solution with black light validation to train compounding and administration staff to use the new CSTD. Each study team's pharmacist monitored the compounding technician by staying in the compounding area and observing actual performance. Monitoring included determining that the CSTD was used correctly, that vials were reconstituted accurately, that doses were compounded correctly, and that compounded syringes contained the amounts specified. The study team nurse monitored the use of the CSTD by the nurse participant and ensured that the parameters for administration of the study doses were met.

A team of 4 certified industrial hygienists (CIHs) was assembled and trained in the study protocol. At least 1 trained CIH participated in the study at each site; the CIHs determined the wipe sampling locations, performed the wipe sampling, and then labeled and logged the samples and prepared them for shipping to the independent laboratory for analysis. The CIHs ensured that wipe samples were stored appropriately prior to shipping and that shipping was done in a timely manner to be certain that samples were received at the independent laboratory within 96 hours of completion of sampling.

Each site provided dedicated time in the compounding and infusion areas for conducting the study. Doses prepared in the sterile products compounding area were dispensed to the nurse to be used in the simulated administration in the infusion area.

Wipe sampling procedure. The wipe samples were collected using TX714A Large Alpha Swabs (ITW Texwipe, Kernersville, NC). Wearing clean gloves, site CIHs dipped a clean swab into the swab wetting solution (50:50 water and methanol). One face of the swab head was pressed against the designated sampling location and wiped in a zigzag pattern, with 2 passes on each swab. Pass 1 was performed top to bottom, and pass 2 was performed left to right with the other face of the swab. The swab head was then inserted into a prelabeled 16-mL glass sample vial, and the swab handle was clipped to an approximately 2.5-cm length and removed. The wipe sampling was repeated with a second swab, and the second swab head was added to the glass sample vial containing the first swab head. The 2 swab heads were analyzed as a single sample. The labeled sample vial was sealed, and the vial identification number, sampling location, surface type, and collection date were recorded on the site sample log. Sample vials were transferred to an insulated cooler with ice packs for shipping. The stability of the cyclophosphamide and fluorouracil samples was determined by the designated testing laboratory (Bureau Veritas North America, Lake Zurich, IL) to be greater than 92% for 9 days under refrigerated conditions. All samples were received by the laboratory within 96 hours of collection. The laboratory is accredited by the Industrial Hygiene Laboratory Accreditation Program (www. us.bureauveritas.com/home/our-services/health_safety_environmental/ laboratories/accreditations).

Analysis of wipe samples. Wipe samples were analyzed for cyclophosphamide and fluorouracil content at the testing laboratory.

All quantitative analyses were conducted on an ABSciex 4000 triple-quad mass spectrometer with electrospray ionization (Sciex, Framingham, MA). The analytic limit of detection (LOD) for each drug was 1 ng per sample, which equated to an LOD of 0.002 ng/cm^2 for each sampled surface.

Recovery. The efficiency of drug recovery from all of the various types of work surfaces encountered in the study was not tested. Recovery efficiencies for similar drugs have been reported to range from as low as 20% on vinyl flooring to 100% on stainless steel.[5]

Recovery of the dedicated stainless steel plates used for sampling was performed by the independent laboratory, which reported the collection efficiency for cyclophosphamide with the solvent and sampling media as approximately 60%, with excellent reproducibility. Fluorouracil collection recovery was reported as 56%, with variable reproducibility. Although recovery efficiencies have been shown to be less than 100% for the drug and surface combinations evaluated in the study, corrections to the reported surface concentrations were not made.

Phase I wipe sampling. Phase I surface wipe sampling was conducted to determine preexisting contamination with cyclophosphamide and fluorouracil. This sampling was done at each participating cancer center to document that the marker AHDs were used at each site, to establish that the site's existing contamination levels were similar to those reported in the literature, and to provide information to the site PIs on the efficacy of their current AHD handling procedures and cleaning practices. Surface locations sampled in compounding areas were selected on the basis of previous research reports.[5,12,15,16] As a wide variety of administration area wipe sampling locations have been described in the literature, in our study the surfaces most likely to be contaminated as a result of leaks during AHD i.v. infusion and i.v. push therapy were selected for wipe sampling; these surface types included stainless steel, laminate or composite surfaces, and vinyl flooring. The study sites provided no information regarding cleaning protocols, when the surfaces had last been cleaned, or how much cyclophosphamide or fluorouracil had been handled prior to sampling. Study sites were requested to do no special cleaning in advance of the wipe sampling but only standard cleaning. The study site CIHs selected and measured sampling locations in the center of the work sur-

face of the class II BSC (2 samples of 500 cm^2 each), on the floor in front of the BSC (1 sample of 500 cm^2), on the floor in the administration area where the i.v. pole with infusion pump for infusing AHDs was usually located (2 samples of 500 cm^2 each), and on the armrest of the chair where AHD patients received therapy (1 sample of 478.5 cm^2).

Phase II wipe sampling (CSTD study protocol). In phase II of the research, the CSTD study protocol was conducted to assess the efficacy of a new CSTD in reducing surface contamination during compounding and simulated infusion of set amounts of the marker AHDs cyclophosphamide

and fluorouracil as specific doses in multiple clinical oncology settings. Phase II wipe sampling was conducted after performing the CSTD study protocol. During phase II protocol validation sampling, surfaces sampled during phase I were cleaned with several solutions previously examined in the literature.[18-21] Multiple wipe samples were collected from each surface and sent for analysis. The results of the analysis showed that the samples were contaminated with cyclophosphamide and fluorouracil above the LOD of the assay, indicating that the surfaces retained the marker AHDs. It was determined that no cleaning method used on the differ-

ent surface types provided a surface free of AHD residue; this finding was consistent with data from other studies reported in the literature.[18-21] As the existing AHD residue would have interfered with the study results, a novel approach was developed to correct this problem and eliminate the variable of preexisting contamination. During the phase II study, new stainless steel plates were placed on each wipe sampling location prior to performance of the CSTD protocol. Plates of 316L stainless steel were cut to 20 × 25 cm (500 cm^2) for use on all sampling locations except for the armrest of the chair, for which a plate measuring 55 × 8.7 cm (478.5 cm^2) was used

Figure 1. For wipe sampling during phase II of the study, stainless steel plates were placed (A) on the surface of the biological safety cabinet (BSC), (B) on the floor in front of the BSC, (C) on the floor near antineoplastic hazardous drug administration, and (D) on the infusion chair armrest.
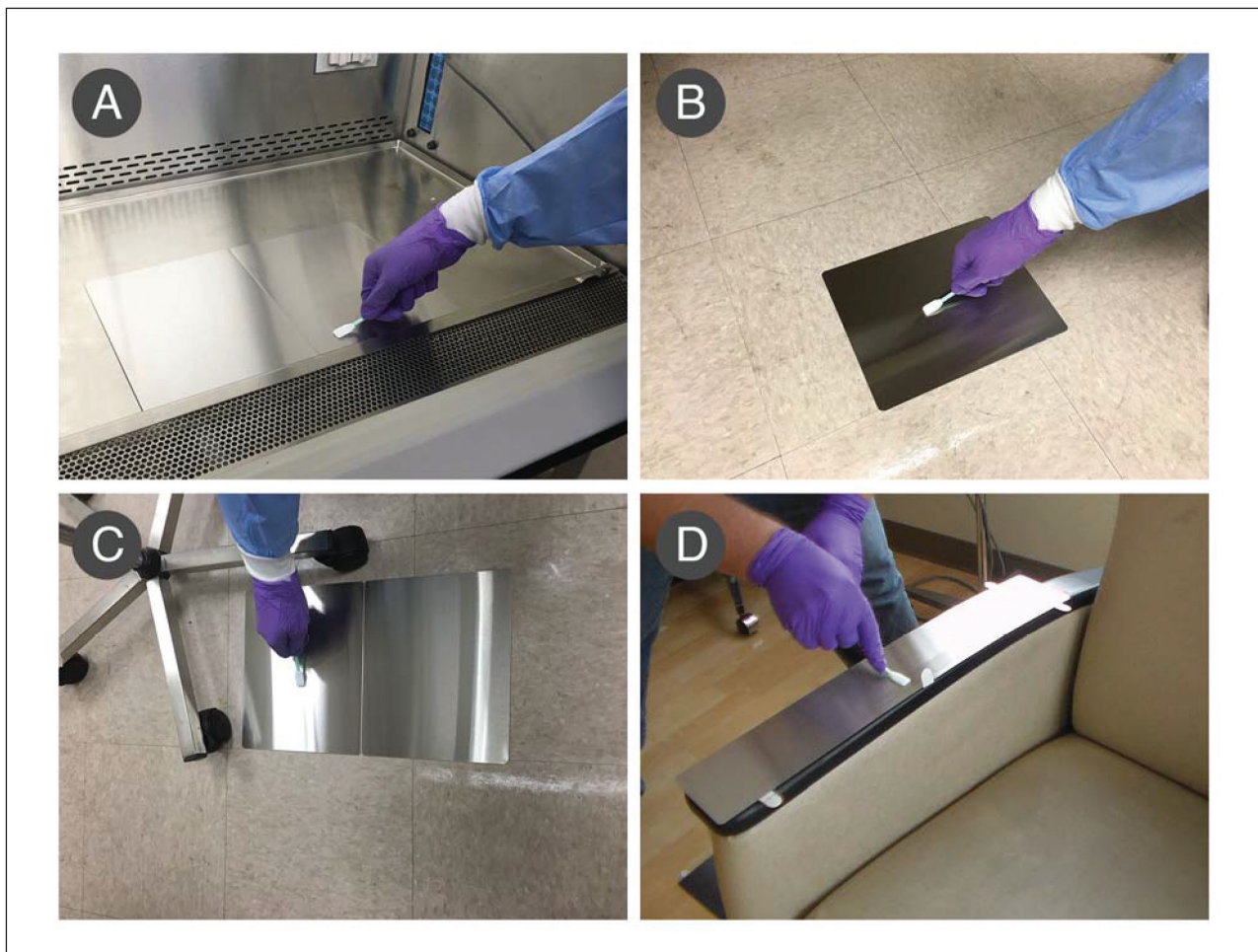
(Figure 1). During compounding, 2 500-cm^2 plates were placed side by side in the center of the class II BSC. All compounding activities were done over the plates. One 500-cm^2 plate was placed on the floor in front of the BSC. The plates were sampled after compounding of cyclophosphamide and fluorouracil was completed, using the wipe sampling procedure described previously.

For simulated AHD administrations, 2 500-cm^2 plates were placed side by side at the base of the i.v. pole with the attached infusion pump, and a single 478.5-cm^2 plate was placed on the armrest of the infusion chair proximal to the i.v. pole prior to connecting AHD preparations to the infusion setup. The plates were sampled using the wipe sampling procedure previously described after the simulated administrations of the i.v. push syringes and the i.v. bag infusion doses of cyclophosphamide and fluorouracil were completed. Fresh plates were used for each sampling location for compounding and administration at each study site.

Tested CSTD. Halo (Corvida Medical, Coralville, IA) is a physical-barrier CSTD that has been cleared by the Food and Drug Administration under the ONB product code for use in the United States. The device has a pressure-equalization containment system that has no vent, valve, or filter (Figure 2). With the Halo system, fluid pathways are established via a single-lumen needle and protected behind sealed membranes at all times. Because the seals are the first components to connect and the last to disconnect, the risks of needle sticks and drug leakage at any point during use of the device are eliminated. The system features a pressure-equalization chamber that is protected and shielded from the user. The device was designed with a focus on ergonomics and ease of use to reduce repetitive motion injury.

Phase II CSTD study protocol. The phase II study protocol, de-veloped to assess the efficacy of the Halo CSTD during compounding and simulated infusion (i.e., doses were not administered to patients) of the marker AHDs cyclophosphamide and fluorouracil, was conducted in multiple clinical oncology settings. The marker drugs were selected on the basis of their common use in the clinical setting, the availability of sensitive analytic methods of detecting surface contamination, and the amount of published data on surface contamination in oncology workplaces with these drugs. Compounding and administration staff wore appropriate personal protective equipment for all processes. Table 2 lists the doses prepared and administered in the CSTD study protocol.

Compounding. Cyclophospha-mide active pharmaceutical ingredient was packaged as 1-g powder-fill, nonsterile vials by the Drug Product Services Laboratory of the University of California, San Francisco. Each vial was washed before being individu-

Figure 2. Components of the Halo test device. Printed with permission of Corvida Medical.
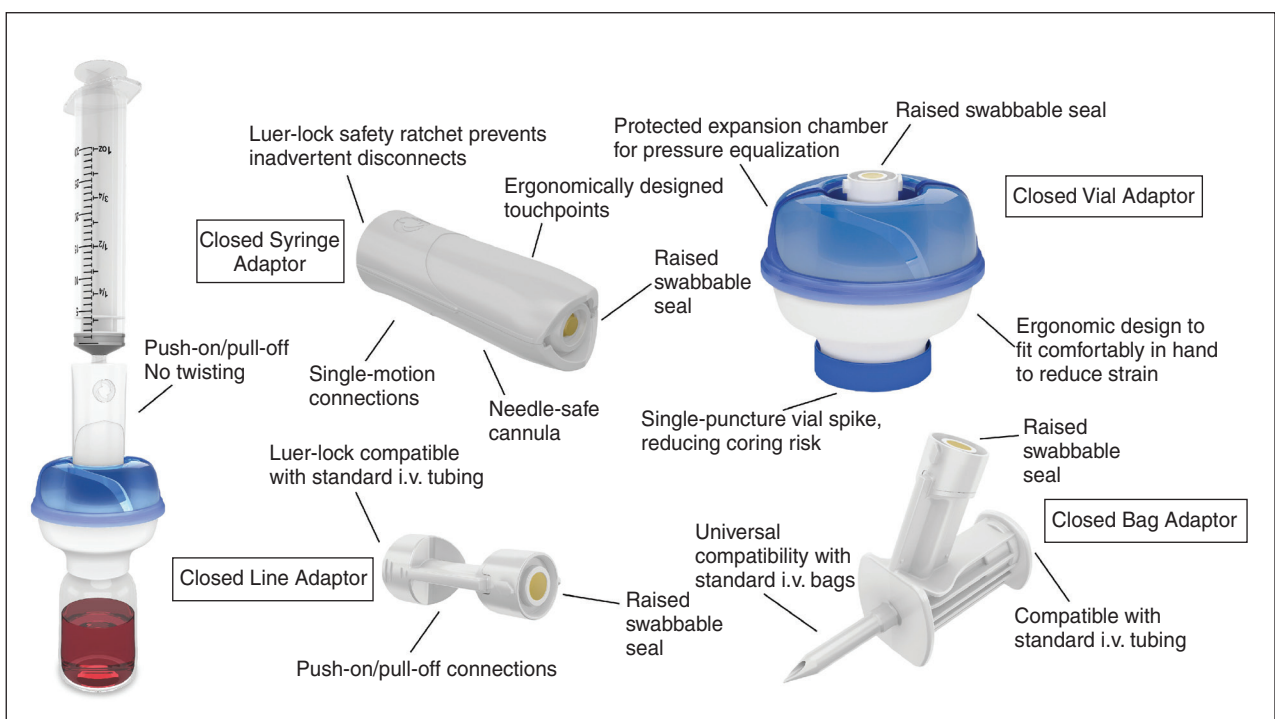
ally packaged in a sealed bag. Commercial fluorouracil, as 500-mg/10 mL vials, was provided by each site from its standard supplier. AHD vials have been shown to be routinely contaminated on the outside with drug residue,[6] which can be transferred to gloves and other surfaces resulting in detectable contamination unrelated to compounding tasks. To avoid this extraneous contamination, cyclophosphamide and fluorouracil vials were cleaned on site using wipers pre-wetted with sodium hypochlorite 0.5% solution (Clorox bleach germicidal cleaner wipes) as described in a recent study.[21] Each vial was further wiped with alcohol and then wipe sampled, and the sample was submitted for analysis to determine the effectiveness of the vial cleaning. All compounding was done in a Class II BSC using aseptic technique and components of the new CSTD.

Ten 1-g cyclophosphamide vials, reconstituted to 20 mg/mL, and 10 0.5-g fluorouracil vials (50 mg/mL) were compounded separately. Compounders used aseptic technique for hazardous drugs, restricting the contents of a syringe to 75% of the labeled quantity; therefore, a 60-mL syringe could contain no more than 45 mL of drug solution. Doses were sequentially compounded, beginning with the liquid fluorouracil, while the cyclophosphamide dissolved. The vials were manipulated to maximize the amount of drug used while reducing the number of syringes and Halo adaptors to stress the device. Large doses were done first, and the remaining drug in vials was used for the smaller doses using the same syringe if possible. Transfers of fluid occurring with the CSTD components were identified and counted to ensure that the protocol was identical at each site. Table 2 identifies the doses compounded and the transfers occurring for each dose.

The protocol required the compounding of 7 doses of cyclophosphamide by transferring 450 mL (9 g) of cyclophosphamide as 10 syringe-to-vial transfers (drug dilution); 14

Table 2. Doses Compounded in Phase II Protocol in Sequential Order

Dose and Sequence of Preparation	No. (Type) of Transfers	Simulated Administration?
Fluorouracil[a]		
1. 900 mg in infusion bag[b]	2 (vial to syringe)	No
	1 (syringe to bag)	
2. 750 mg in 30-mL syringe	2 (vial to syringe)	Yes
3. 600 mg in 30-mL syringe	2 (vial to syringe)	No
4. 2.25 g in infusion bag[b]	5 (vial to syringe)	Yes (over 30 min)
	1 (syringe to bag)	
Cyclophosphamide[c]		
5. 2.7 g in infusion bag[d]	3 (vial to syringe)	Yes (over 45 min)
	3 (syringe to bag)	
6. 800 mg in infusion bag[d]	1 (vial to syringe)	No
	1 (syringe to bag)	
7. 600 mg in infusion bag[d]	1 (vial to syringe)	No
	1 (syringe to bag)	
8. 1.7 g in infusion bag[d]	2 (vial to syringe)	No
	2 (syringe to bag)	
9. 400 mg in 60-mL syringe	2 (vial to syringe)	Yes
10. 2.4 g in infusion bag[d]	3 (vial to syringe)	No
	3 (syringe to bag)	
11. 400 mg in 30-mL syringe	2 (vial to syringe)	Yes

[a]Fluorouracil used as 50-mg/mL solution in 10-mL vials.
[b]Added to 250-mL infusion bag containing 0.9% sodium chloride injection.
[c]Cyclophosphamide prepared as 20-mg/mL solution from dilution of 10 1-g vials (10 syringe-to-vial transfers)
[d]Added to 500-mL infusion bag containing 0.9% sodium chloride injection.

vial-to-syringe transfers as drug withdrawal, when the CSTD syringe adaptor engages the CSTD vial adaptor; and 10 syringe-to-bag transfers of 45 mL or less. Four doses of fluorouracil were compounded by transferring 90 mL (4.5 g) of drug solution from 10-mL vials as 11 vial-to-syringe transfers and 2 syringe-to-bag transfers. Drug volumes requiring 2 vials resulted in multiple transfers; retrieving remaining drug from a partial vial is another transfer. Wipe sampling was done on the stainless steel plates after all compounding was completed and waste was contained and removed.

Administration. Administration was done in the previously sampled AHD infusion area at each study site using a simulation method that did

not involve patients. An infusion pump provided by the cancer center, with a primary pump set connected to an infusion bag of 0.9% sodium chloride injection, was set up to simulate administration. The end of the set was attached to a 3-L sterile, empty i.v. compounding bag using a 16-gauge needle, and the connections were secured with duct tape. The 3-L sterile, empty i.v. bag used as a receptacle for the infused AHD doses was placed into a lined plastic waste container. The infusion setup was checked for leakage using primary solution prior to commencement of the administration phase of the study protocol. Upon protocol completion, the 3-L sterile i.v. bag was wrapped in a plastic bag and discarded as bulk chemotherapy waste.

Two administration trials were done sequentially, with no sampling or cleaning performed between. The i.v. bag doses for the trial were infused through the site-specific infusion pump over 30–45 minutes (Table 2). On completion of each infusion, the infusion bag and secondary i.v. set were disconnected from the CSTD line adaptor at the primary i.v. pump set Y site. The i.v. push dose was then administered by connecting the syringe with the CSTD syringe adaptor to the CSTD line adaptor attached to the lower Y site. When the infusion was completed, the syringe was disconnected from the CSTD line adaptor with the CSTD syringe adaptor still attached to the syringe. The CSTD line adaptor was left attached to the primary pump set. Waste was placed into a chemotherapy transport and/or waste bag and sealed. Wipe sampling was done on the stainless steel plates after all simulated administrations were completed and waste was contained and removed.

Statistical methods. Levels of contamination (expressed in nanograms per square centimeter) among the 6 surfaces at each study site and among the 13 study sites were compared during both the phase I (prestudy) and the phase II (CSTD protocol) sampling periods using nonparametric analysis of variance (a Kruskal–Wallis test), with Dunn's test used for multiple post hoc comparisons. Because BSC sampling during both phases of the study involved sample collection from surfaces of equivalent area and composition (i.e., stainless steel), phase I versus II study contamination of BSC surfaces was evaluated using Wilcoxon's signed rank test to determine if the median level of contamination in phase I or phase II was different from 0.001 ng/ cm^2, or 50% of the LOD. The frequencies of contamination in pharmacy versus drug administration areas were evaluated by Fisher's exact test. All analyses were performed using GraphPad Prism (GraphPad Software,

Inc., La Jolla, CA). The a priori level of significance was 0.05.

Results

The results of the phase I and II contamination studies are presented in Tables 3 and 4, respectively. During the study period, 156 samples were collected from 13 U.S. study sites during each phase of the study. Every sample collected was analyzed for both of the study drugs. Table 3 shows the amounts of each study drug measured during phase I, representing the preexisting contamination of 6 surface locations within the aggregate of 13 study sites. Table 4 reports only data on measured contamination of wipe samples collected from the same study sites and surface locations during phase II (CSTD protocol) sampling using pristine stainless steel plates, set drug amounts, and specific doses.

No significant differences were observed in the level of study-drug contamination among the 6 surfaces tested across all 13 study sites during either the phase I or the phase II study. There were, however, differences in contamination between various study sites (Table 3). For the phase I (preexisting contamination) study, post hoc comparisons indicated that significance was due to site 4 for cyclophosphamide ($p = 0.001$) and sites 4, 16, and 18 for fluorouracil ($p < 0.0001$). In contrast, the phase II study comparisons (Table 4) found no significant differences among study sites ($p = 0.08$ for cyclophosphamide and $p = 0.05$ for fluorouracil).

In aggregate, results of wipe sampling at the 13 study sites during phase I of the study indicated a high frequency of preexisting contamination, with 66.7% of samples (104 of 156) testing at or above the LOD (0.002 ng/cm^2) for 1 or both of the study drugs (Table 3). Of the surface samples tested in phase II after execution of the defined CTSD protocol, 5.8% (9 of 156) had detectable levels of 1 or both of the study drugs (Table 4). However, with the exception of 2 positive BSC samples at site 19, the level of con-

tamination was very low (i.e., detected amounts of the marker drugs were at or only slightly above the LOD for the remaining 7 samples).

Because BSC surface composition and sampling areas were equivalent across the study sites for both the phase I and phase II sampling periods, the left and right BSC wipe areas were further evaluated to determine if contamination was significant (at the $p < 0.05$ level) relative to a value of 50% of the LOD, or 0.001 ng/cm^2. The results indicated that there was significant residual contamination from 1 or both study drugs at both BSC sampling locations prior to the phase II study, whereas the level of contamination after the use of the CSTD in phase II was not significantly different from a value 50% below the LOD ($p = 1.0$).

In contrast to other published studies,[5,11] our study found that preexisting contamination in the compounding areas was less than in the administration areas. The aggregated results of phase I wipe sampling at the 13 study sites showed that 55.1% of samples (43 of 78) from compounding areas and 78.2% of samples (61 of 78) from administration areas tested above the LOD for 1 or both study drugs ($p = 0.004$). For the surfaces tested after performance of the defined phase II CSTD protocol, this difference was not significant, with 8.9% (7 of 78) of samples from the compounding areas and 2.6% (2 of 78) of samples from the administration areas testing at or above the LOD for 1 or both study drugs ($p = 0.17$).

Onsite cleaning of the drug vials used in the study was done to reduce the extraneous drug residue found on most AHD vials.[6] Vials were sampled after cleaning to determine if residual drug remained on the vial surfaces. The data from the 13 sites represented 65 vial-pair samples per drug. Despite precleaning, 9 of 65 cyclophosphamide vial pairs (13.8%) and 19 of 65 fluorouracil vial pairs (29.2%) were found to have levels of contamination above the LOD for the assay. The sampled vial surface area

was not measured during sampling, so the contamination was not quantifiable in terms of nanograms of drug per square centimeter.

Discussion

The primary purpose of the study was to evaluate the performance of a new CSTD in reducing surface contamination during compounding and simulated administration of AHDs. The study entailed surface wipe sampling and analysis for the marker AHDs cyclophosphamide and fluorouracil using a specific and robust protocol executed in a cohort of 13 U.S. cancer centers. The protocol required that set amounts of study drugs be compounded and "administered" over a short period of time using 30- and 60-mL syringes fitted with the components of the Halo CSTD. The protocol was designed to provide comparative data from all participating study sites.

Comparison of the wipe sampling data in the phase I (Table 3) and phase II (Table 4) studies showed a significant decrease in overall surface contamination with use of the Halo CSTD. Although the investigation described here was not a "head-to-head" study of pre- and post-CSTD implementation contamination levels, the wipe sampling data showed that use of the Halo device was an effective method of reducing and containing surface contamination not only in the compounding of AHDs but also in their administration.

The phase II study protocol was designed to minimize variations among study sites to allow strong site-to-site comparisons. This level of standardization is not evident in reports on other CSTD studies in the literature. In most published studies, researchers sampled different surfaces depending on the design of the compounding area[5,10-12,13]; many selected surface areas of various sizes for wipe sampling, even within the same sampling location[11,12,13,15,16]; and some did not report the measurements of the sampled areas.[11,12,15,16] The amount of

Table 3. Preexisting Surface Contamination by Cyclophosphamide and Fluorouracil in Pharmacy and Administration Areas[a]

| Site No. | Contamination Level in Pharmacy (ng/cm²) | | | | | | Contamination Level in Administration Areas (ng/cm²) | | | | | | % Results ≥ Drugs' LOD |
| | BSC, Floor | | BSC, Left | | BSC, Right | | Floor, Right | | Floor, Left | | Chair Arm | | |
	CP	5FU	CP	5FU	CP	5FU	CP	5FU	CP	5FU	CP	5FU	
3	0.029	0.290	0.003	ND	0.003	ND	0.004	0.112	0.006	0.145	0.015	0.598	83
4	0.648	6.440	0.051	0.168	0.052	0.132	0.086	0.600	0.056	0.270	0.028	0.069	100
6	0.061	ND	ND	ND	ND	ND	0.007	0.025	0.005	0.013	0.021	0.034	58
8	0.126	0.516	0.035	19.880	0.031	2.960	0.005	0.013	0.005	0.010	0.005	0.056	100
9	0.003	ND	ND	ND	ND	ND	ND	0.003	ND	ND	0.007	0.007	33
10	ND	ND	ND	0.006	ND	ND	ND	0.288	0.083	0.100	0.007	ND	50
12	0.018	0.212	0.004	0.045	0.003	0.037	ND	0.004	ND	ND	ND	ND	58
13	0.024	0.009	0.048	0.046	0.336	0.047	0.021	0.005	0.036	0.009	0.004	0.014	100
14	ND	ND	0.007	ND	0.012	ND	0.012	ND	0.007	ND	0.007	ND	42
16	0.010	0.120	ND	0.127	ND	0.158	0.246	3.480	0.023	3.880	0.270	0.301	83
17	ND	ND	ND	ND	ND	ND	0.002	ND	ND	ND	ND	0.006	17
18	0.110	3.020	0.018	0.668	0.017	1.144	0.018	0.988	0.021	0.664	0.010	0.089	100
19	ND	ND	ND	ND	ND	ND	0.360	ND	0.042	0.019	0.028	0.004	42
Median[b]	0.018	0.009	0.003[c]	0.006[c]	0.003[d]	<0.002[e]	0.013	0.019	0.014	0.016	0.007	0.014	...[f]

[a]BSC = biological safety cabinet, LOD = limit of detection, CP = cyclophosphamide, 5FU = fluorouracil, ND = not detected.
[b]Calculated for values exceeding LOD of 0.002 ng/cm².
[c]p = 0.016 for comparison of median contamination level in the BSC with 0.001 ng/cm² (50% of LOD) using Wilcoxon signed rank test.
[d]p = 0.022.
[e]p = 0.031
[f]Not applicable.

Table 4. Contamination by Marker Drugs in Pharmacy and Administration Areas After CSTD Use[a]

| | Contamination Level in Pharmacy (ng/cm²) | | | | | | Contamination Level in Administration Areas (ng/cm²) | | | | | | |
| | BSC, Floor | | BSC, Left[c] | | BSC, Right[c] | | Floor, Right | | Floor, Left | | Chair Arm | | % Results ≥ Drugs' LOD |
Site No.[b]	CP	5FU	CP	5FU	CP	5FU	CP	5FU	CP	5FU	CP	5FU	
8	ND	ND	ND	ND	ND	ND	0.002	ND	ND	ND	ND	ND	8
9	ND	0.002	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	8
14	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.003	8
17	ND	0.002	ND	0.003	ND	0.003	ND	ND	ND	ND	ND	ND	25
18	ND	0.004	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	8
19	ND	ND	2.600	ND	0.386	ND	ND	ND	ND	ND	ND	ND	17

[a]CSTD = closed system drug-transfer device, BSC = biological safety cabinet, LOD = limit of detection, CP = cyclophosphamide, 5FU = fluorouracil, ND = not detected.
[b]Sites 3, 4, 6, 10, 12, 13, and 16 had no detectable contamination.
[c]p = 1.0 for comparison of median contamination level for either drug in the BSC with 0.001 ng/cm² (50% of LOD) using Wilcoxon signed rank test.

marker drug handled during the study period was frequently not reported or was "normalized" from historical data.[5,11,12,15,16] Some researchers have conducted studies at sites that handle small amounts of marker drug and have reported low surface contamination rates after an intervention,[13] in some cases providing what we believe to be misleading conclusions regarding the impact of CSTD use on contamination rates.

NIOSH is attempting to develop a protocol to test the containment performance of both the physical-barrier type of CSTD and devices designed to operate using air-cleaning technologies.[22,23] Difficulties encountered in this attempt include the selection of a nontoxic chemical or drug that can be a substitute or surrogate for a hazardous drug and the method of capturing and analyzing the surrogate. The planned NIOSH protocol will be a positive step in evaluating these devices. The protocol described in this study addresses the need to evaluate not only CSTD performance but also worker interaction with the CSTD in "real-world" situations. As the effectiveness of a CSTD can be influenced by worker practice, a device's ease of use and acceptance by workers are important considerations.

The results of study phase I (Table 3) showed a range in the amount of preexisting surface contamination by the marker drugs at the 13 study sites similar to ranges reported in other multisite studies.[15,16] As in these other studies, we made no attempt to address the amount of the marker drugs used prior to sample collection in order to determine preexisting contamination or to correct for cleaning or other work practices in phase I. However, we used a unique approach to control for preexisting AHD surface contamination in phase II and the inability to clean the surfaces after wipe sampling in phase I. This approach involved the use of custom stainless steel plates as surface templates in the CSTD protocol phase of the study. These plates were made from the same stainless

steel as the surfaces of the BSC and allowed for direct comparison of BSC surface contamination levels during compounding in phases I and II.

The results of phase II (Table 4) showed an overall reduction in surface contamination by the study drugs cyclophosphamide and fluorouracil at each site. After the completion of the phase II study protocol, which required the use of a fixed amount of the marker drugs and a clean stainless steel template, the aggregate median contamination level for both study drugs at the 13 study sites was less than 0.002 ng/cm^2 on both the BSC work surface and the floor in the compounding area.

A number of wipe sampling studies involving the use of a CSTD for compounding marker drugs have been published in the peer-reviewed literature.[12,15,16] Several studies used similar wipe sampling procedures and sample analysis to assess cyclophosphamide contamination on work surfaces.[12,15,16] The efficiency of cyclophosphamide recovery from surfaces sampled in those studies was greater than 80%.[15] The analytic LOD for cyclophosphamide was 0.10 ng/mL, allowing de-

tection of 16 ng of cyclophosphamide per sampling surface.[12,15] Three multisite studies of the PhaSeal CSTD[12,15,16] were sufficiently similar to our study in methods and reporting of results to allow a comparison of that device and the Halo device (Table 5).

The study described here was the first to focus on measuring existing surface contamination in AHD infusion areas, where spills and leaks at the delivery site are likely to occur, and to assess the performance of a CSTD directly at those sites. In wipe sampling studies done in AHD compounding areas, sampling locations have been fairly uniform, usually including the surface of the BSC and the floor in front of the BSC. In contrast, studies of administration areas have been very inconsistent as to the exact locations of wipe sample collection. This inconsistency may be the result of the variety of available AHD infusion scenarios, which include bedside infusions for inpatients and armchair infusions for outpatients. In the CSTD studies discussed here, investigators sampled various sites in drug administration areas, including floors, counters, drug storage areas, and waste bins.

As the literature was not helpful in selecting administration area sampling locations for our study, input from experienced oncology infusion nurses was used to determine the locations that would most likely be affected by the use of a CSTD. The armrest of the infusion chair, which typically lies directly under the infusion pump hanging on the i.v. pole, and the floor under the i.v. pole were considered likely to be the locations most highly contaminated by fugitive AHD released during the administration process. The 13 study sites all had infusion armchairs with armrests, i.v. poles, and infusion pumps. The results of the phase I analysis of preexisting surface contamination of the infusion chair armrest and the floor under the i.v. pole at each study site demonstrated that 78.2% of wipe samples (61 of 78) were above the LOD. The percentage of positive wipe samples was higher than values reported in previous studies of administration areas,[5,11] probably due to other researchers' selection of locations directly adjacent to AHD infusion areas.

Our study focused on the AHD administration area for evaluation of sur-

Table 5. Comparison of Cyclophosphamide Surface Contamination in Selected CSTD Studies[a]

Variable	Ref. 12	Ref. 15	Ref. 16	Current Study
Yr published	2006	2011	2013	2018
No. sites	3	22	30	13
CSTD tested	PhaSeal	PhaSeal	PhaSeal	Halo
Cyclophosphamide usage	58.3 g/wk	NR	NR	10 g in 1 hr
Median contamination level, ng/cm^2 (range)				
Floor in front of BSC[b,c]	0.0055 (NR)	0.01 (<0.01–16.33)	0.08 (<0.01–4.13)	<0.002 (all < LOD)[d]
BSC surface[b]	0.0288 (NR)	0.02 (<0.01–5.41)	0.02 (<0.01–38.59)	<0.002 (<0.002–2.60)[d]
Approximate sample area, cm^2	500 max	300–11,050	NR	500
Recovery efficiency, %	80	80	80[e]	60
LOD, ng/sample	16	16	16[e]	1
Study period for CSTD use	2 wk	Snapshot after several mo	Snapshot after >6 mo	~1 hr

[a]CSTD = closed system drug-transfer device, NR = not reported, BSC = biological safety cabinet, LOD = limit of detection.
[b]May include residual contamination from prior use.
[c]Recovery from floor material may be much less.
[d]Clean templates used for sampling.
[e]Results from reference 15.

face contamination before and after implementation of a CSTD protocol at multiple sites in a comparative study. With the current mandate of *USP* general chapter 800 that CSTDs must be used during administration of AHDs,[24] a study to validate the effectiveness of CSTDs in infusing AHD doses from i.v. infusion bags and i.v. push syringes is a critical step in selecting a CSTD.

Although the primary concern in selecting a CSTD should always be its ability to contain AHD residue during compounding and administration, staff acceptance of the device may influence CSTD performance in practice. CSTDs have been studied for their impact on workload, staff acceptance, and ease of use.[25-27] These issues were addressed during our 13-center study using a questionnaire. Participating clinicians at each site were asked to rate the Halo CSTD for ease of use on a 5-point scale (1 = extremely dissatisfied, 5 = extremely satisfied). Of the total of 26 clinicians who responded to the questionnaire, 18 gave the Halo device a score of 5, with the other 8 clinicians giving it a score of 4. Details regarding responses to the questionnaire will be presented in a future article.

Our study examined surface contamination in a variety of U.S. cancer treatment centers where AHDs are compounded and administered. Although the 13 centers may not be representative of all such centers in the United States, the levels of preexisting contamination by the study drugs reported in these 13 centers were very similar to those described in a number of published U.S. studies.[5,11,15,16] The limitations of wipe sampling studies, in general, have been recently discussed by Connor et al.,[28] who noted that sampling of smaller surface areas may allow contamination to go undetected. For our study we selected sampling locations consistent with those targeted in other investigations and chose 500 cm^2 as an acceptable sampling area. Further studies may be needed to document the effectiveness of the selected sampling methods.

Our study involved use of a surface wipe sampling method and a solvent not previously reported in the AHD literature. As noted above, the efficiency of cyclophosphamide collection from stainless steel with the solvent and sampling media used was approximately 60%, and fluorouracil recovery was reported as 56%. The recovery efficiency was less than that of some methods reported in similar studies[12,15,16]; the analytic LODs (1 ng of either marker drug per wipe sample) in our study were, however, superior, which we believe partly offsets the relatively low recovery efficiency.

Other limitations of the study included the presence of AHD residue on drug vials as received from the manufacturers.[6] Despite precleaning, a substantial proportion of our vial pairs were found to have levels of contamination above the LOD. This contamination was not quantifiable as nanograms per square centimeter, but the finding of fewer incidents of cyclophosphamide versus fluorouracil vial contamination was probably due to the prerinsing done by the production pharmacy before packaging the individual vials into plastic bags for shipping. These results agree with findings reported by other investigators, who found that no method of vial cleaning has been shown to remove 100% of measurable contamination.[6,21] In addition, there was cross-contamination of 2 vial pairs (i.e., cyclophosphamide was found on a fluorouracil vial sample, and fluorouracil was detected on a cyclophosphamide vial); this was probably due to vial-to-vial transfer during handling at the site, as the cyclophosphamide vials were presumably produced in an area where exposure to fluorouracil could not occur. Transporting vials of different drugs together or storage of different drugs in bins just prior to compounding, however, may result in this type of cross-contamination. Transfer of contamination from gloves to other surfaces may also be responsible.

No studies have proved that using a CSTD eliminates exposure to AHDs.

The best that any intervention study has shown is that there is frequently a statistically significant reduction in AHD surface contamination with the use of certain CSTDs during compounding and administration of marker AHDs. It is a reasonable assumption that reduction in the amount of AHDs on work surfaces should reduce the amount of drug residue available to be incorporated into the body via dermal uptake or hand-to-mouth contact. As all devices marketed as CSTDs in the United States have not been tested in peer-reviewed, published studies, it is paramount for potential users to follow the *USP* general chapter 800 recommendation to "carefully evaluate the performance claims associated with available CSTDs based on independent, peer-reviewed studies."[24]

Conclusion

A study involving a rigorous protocol and 13 cancer centers across the United States demonstrated that the CSTD reduced surface contamination by cyclophosphamide and fluorouracil during compounding and simulated administration. Participants reported that the CSTD was easy to use.

Additional information

The content of this manuscript is solely the responsibility of the authors and does not

necessarily represent the official views of NIH.

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