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Evaluation of the hazardous drug surface contamination in pharmacy compounding and administration clinical setting after adoption of standardized cleaning workflow and a closed system transfer device

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Abstract

Objectives: The compounding and administration of hazardous drugs present a potential risk to healthcare worker and patient safety. This study sought to evaluate the HD surface contamination in multiple pharmacy and nursing areas that include standardized cleaning techniques and utilization of closed system transfer devices.
Methods: This study was conducted at six different areas in the pharmacy and nursing areas. Each area was assessed three times for five different HD's surface contamination at an initial, 3 month, and 6 month follow up. Hazardous drug surface testing was performed for five most compounded HDs. A total of 90 individual samples were taken and analyzed during the study.
Results: A total of 30 samples were collected at three different timepoints for a total of 90 individual samples and analysis results. All 90 samples were negative (below the lower limit of detection; 0.01 ng/cm^2), for their respective drug residue.
Conclusions: The method and design described in this evaluation may offer a way to determine if a facility's current HD work practices and controls retain reduced HD surface contamination based upon published threshold values. Adoption and utilization of standardized work, including use of a closed system transfer device, and cleaning practices, described in this study, may present an option for facilities to retain reduced HD surface contamination, based upon previously determined threshold values.

Keywords: antineoplastic agents; ChemoClave; ChemoLock; closed system transfer device; drug compounding.

Introduction

The risks of occupational exposure to hazardous drugs (HD) have been known for decades. Occupational exposure to healthcare workers may occur at any point during the drug receipt, preparation, compounding and administration areas and processes. These exposures may lead to serious adverse reactions including but not limited to asthma, birth defects, miscarriages, and cancer [1].

Although this information was publicly available as distant as the 1970s, studies continue to show that surface contamination for HDs is persistent and widespread through both the pharmacy and nursing areas, potentially exposing healthcare workers to adverse reactions. Widespread surface contamination from multiple antineoplastic agents on a variety of surfaces in the pharmacy preparation and administration areas in six different centers in the USA and Canada has been reported with significant measurable amounts in 75% of the pharmacy and 65% of the administration area samples [2]. These results have been repeated, with lower detection rates but still considerable by investigating the environmental contamination of cyclophosphamide, ifosfamide, and methotrexate in pharmacy and patient areas, finding positive samples (52%, 20%, 3% respectively) for each measured HD [3]. Cyclophosphamide has been described as potentially the most prevalent environmental contamination of HDs in oncology pharmacies and outpatient clinics in Canada as part of a surveillance project also finding that cyclophosphamide was the HD most often found in the surface samples (32.4% of samples with positive result), followed by gemcitabine (20.3%) [4]. Similar results were found in which biological and environmental

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exposure to cyclophosphamide in nurses was evaluated and determined that elevated levels were present in one third of the participating nurses [5].

Although these studies show the continued consistency of HD surface contamination; the situation may be more serious than previously anticipated since each of these studies were limited in the number of HDs evaluated. Other HDs, not sampled, in these and other studies, may well be present.

Evidence of persistent and widespread HD surface contamination has led researchers and hospitals to implement surface wipe sampling as part of the standard workplace environmental monitoring procedures. But, as in previous decades, published studies continue to show that consistent contamination and the potential for worker exposure remains, as does the surface contamination of HDs. Published studies have indicated that standard cleaning procedures may not be sufficient to decrease or eliminate the HD surface contamination to acceptable levels. Previous evaluations have determined that 14 out of 23 surfaces sampled (61%) prior to current cleaning practices were contaminated with methotrexate or cyclophosphamide and while the post-clean contamination levels were generally lower, the concentration of the methotrexate was similar, and some samples had higher post-clean contamination levels [6].

Development of guidance, safe handling precautions, and environmental and engineering controls have occurred but, concentration of HD surface contamination continues to be reported in healthcare settings globally and at multiple timepoints throughout the production, receipt, preparation and compounding, and administration of hazardous [7–16].

Multiple cleaning agents have been investigated for their effectiveness in eliminating HD surface contamination [17, 18]. In conjunction with the knowledge that no single product or formulation has been proven to be 100% effective in the removal of antineoplastic contamination on work surfaces, the decontamination of HD requires continuous efforts or knowledge of the presence of an HD contamination and further highlight the benefits of preventative controls.

Guidance on the assessment and controls recommended to reduce exposure of HDs are widely available from institutions such as: OSHA and NIOSH. To further enhance protection of healthcare workers against potentially hazardous exposures during the compounding and administration, USP 800 Chapter includes a section on containment supplemental engineering controls such as the use of closed system drug transfer devices (CSTDs) that mechanically prohibit the transfer of environmental contaminants into the system and the escape of the HD or vapor concentrations outside the system. The use of CSTDs have become accepted as part of HD safety programs and used in conjunction with engineering controls.

Although published studies indicate that the implementation of CSTDs, along with standard work practices, may help to eliminate or reduce accidental exposure the HDs [19–26], including evidence that indicates that the CSTD alone, may help to reduce the potential exposure [23], the implementation cost and lack of regulatory compliance or requirements, especially in emerging countries, may hamper their adoption.

Objectives

This study sought to survey potentially high-risk surfaces for HD surface contamination to determine the level of effectiveness of current work practices and procedures for cleaning and decontaminating in minimizing HD surface contamination, based upon previously published threshold values (at or below 0.01 ng/cm^2) [2]. The areas evaluated included the continued implementation of a secondary control in the form of closed system transfer devices (ChemoLock and ChemoClave, ICU Medical, San Clemente, CA, USA), which is designed to reduce or eliminate HD surface contamination This routine evaluation included multiple functional areas, representing both the nursing and administration clinical settings.

This study may also present a method for the routine evaluation of surface contamination to verify that selected areas are free from HD contamination and further identify opportunities for updating cleaning procedures or other environment or facility controls to improve the ability to limit or eliminate HD surface contamination.

By demonstrating the effectiveness of the work practices of the facility, and the controls that are utilized in the preparation and administration of HDs, this may offer a solution by which facilities which struggle or are investigating the modification of work practices to reduce staff or patient exposure to HDs.

Material and methods

Evaluated environment – compounding and nursing

The test areas that were analyzed were based upon several factors. Firstly, all the areas analyzed had significant potential exposure to HDs and were of high concern for HD leakage or accidental spill. The areas also represented surfaces which may have prolonged exposure to HD containers and may offer an increased chance of significant detection. These areas sought to replicate worst case scenarios by

which the work practices and controls incorporated into the procedures would be most challenged.

The compounding environment tested included the biological safety cabinet hood and pharmacy pass thru to nursing area in the Cancer Center Pharmacy as well as the staging counter in HD buffer room and pharmacy pass thru in main pharmacy HD compounding suit.

The Nursing staging area in the Cancer Center infusion suite and the chemotherapy storage bin on inpatient oncology nursing floor were tested.

CSTD devices

The ChemoLock and ChemoCLave are needlefree, single-use, CSTDs. These devices have been incorporated into practice in both the preparation and administration areas. The CSTDs have a mechanical means to prevent the transfer of environmental contaminants into the system, and the escape of HD or vapor concentrations outside the system. The systems include closed vial and bag access devices, a closed syringe adapter and closed patient administration sets. All components of the system include passive, self-sealing mechanisms which cannot be deactivated and remain protective through disposal.

Both ChemoLock and ChemoClave CSTDs are designed to prevent the transfer of environmental contaminants into the system and the escape of drug or vapor concentrations outside the system. The ChemoLock utilizes a click-to-lock design which keeps the connection secure while an integrated membrane-to-membrane seal creates a mechanically closed system. The ChemoClave uses a luer-based connection to secure the connection and retain the closed system. Both have received FDA clearance as "Closed System Transfer Devices", under classification product code ONB (Closed Antineoplastic and Hazardous Drug Reconstitution and Transfer System).

Hazardous drug compounding was performed using the ChemoLock CSTD for cyclophosphamide and paclitaxel. For the other studied HDs (fluorouracil, methotrexate, and doxorubicin), these are prepared using a kit that includes the ChemoClave vial adapter and male luer connector (Spiros, ICU Medical, San Clemente, CA, USA).

Intravenous or subcutaneous administration utilized the ChemoClave with the male luer on the distal end of the secondary tubing. For HD delivery for secondary administration a ChemoLock secondary tubing set, which has a ChemoLock port at the proximal end and a bonded male luer on the distal end of the tubing set.

Standardized cleaning procedures

All areas, except for the staging counter in main pharmacy HD buffer room, are cleaned by separate daily and monthly cleaning procedures. The main pharmacy HD buffer room receives an additional weekly cleaning.

The agents utilized for cleaning of the surfaces are a broad-spectrum bactericidal and general virucide (PREempt RTU Disinfectant Solution, Contec, Inc, Spartanburg, SC, USA) and 70% isopropyl alcohol.

The daily cleaning for the surfaces sampled require two applications of the broad-spectrum agent, followed by one application of sterile alcohol. The daily cleaning for the surfaces sampled was performed once in the morning prior to compounding and administration activities and again after all compounding and administration activities were complete.

The monthly additional cleaning includes the same procedure of the daily with the addition of one application of another broad-spectrum disinfectant (Peridox Disinfectant, Contec, Inc, Spartanburg, SC, USA) that also contains sporicidal characteristics. The use of these products is supported by work identifying those solutions containing 10^{-2} M anionic surfactants and 20% isopropyl alcohol have been demonstrated to be most effective in the removal of HD surface contamination [17]. Cleaning is performed by trained pharmacy and hospital staff, at regular timepoints. All cleaning agents are allowed to sit on the surfaces for the recommended period of time and then removed via wipes.

There were no modifications to the standard cleaning procedures or frequency throughout the course of the study.

Standardized work practices

Procedure: This environmental wipe sampling was conducted in six areas that included pharmacy and nursing in select locations with five HDs in six different locations in order to assess a baseline level contamination, and subsequent follow up surface wipes to assess surface contamination in the same sample locations with the same HDs in accordance with Table 1, below.

The initial (t=0) surface wipe sample collection coincided with the opening of the new pharmacy area. No HDs had been handled in the pharmacy prior to the initial sample collection for the pharmacy areas in the Cancer Center. For all other areas, the wipe samples were conducted after compounding or handling was performed, including the five HDs sampled in the study. For all collections, except for the samples taken from the initial pharmacy testing, the samples were collected midday, between standard compounding and administration activities and standard cleaning activities. Images displaying the areas and demarcation of areas to be sampled are shown in Figures 1, 2 and 3, below.

There was a total of two follow up surface wipe sample collections. The follow up surface wipe collections were conducted at 3 months and 6 months after the initial surface wipe sample collection and followed the same sampling patterns as the initial surface wipe sampling.

Table 1: Drug and sample location.

Hazardous drugs	
Paclitaxel	Fluorouracil
Cyclophosphamide	Methotrexate
Doxorubicin	
Sampling locations	
Biological safety cabinet ISO 5 in cancer center pharmacy (type 304 stainless steal)	Cancer center pharmacy pass thru to nursing medication room (stainless steal or epoxy-painted stainless steal)
Nursing staging counter in patient infusion room (corian countertop)	Main pharmacy pass thru (stainless steal or epoxy-painted stainless steal)
Staging counter in main pharmacy HD buffer room (stainless steal)	Inpatient Chemo receiving bin on oncology nursing floor (ultra high-density virgin polypropylene plastic- non-PVC)

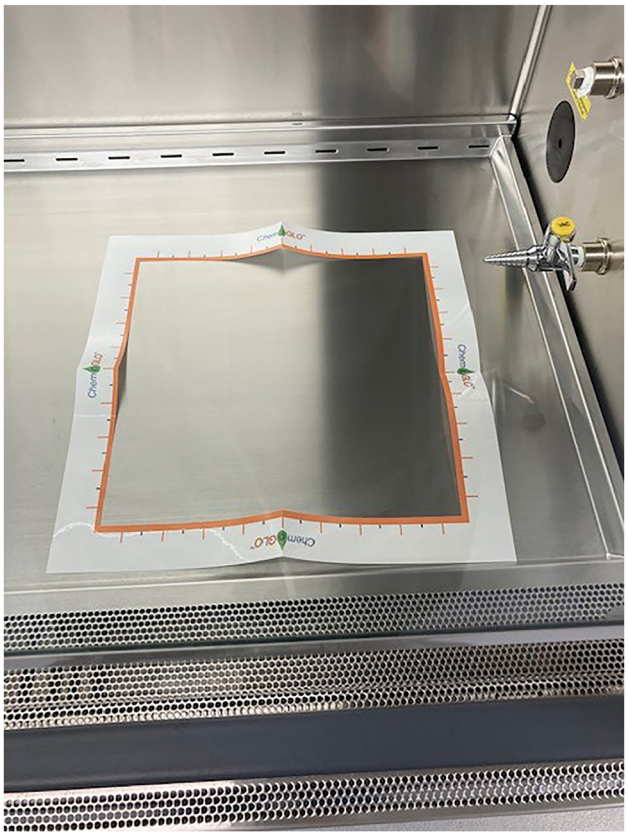

Figure 1: HD sampling area inside the BSC.

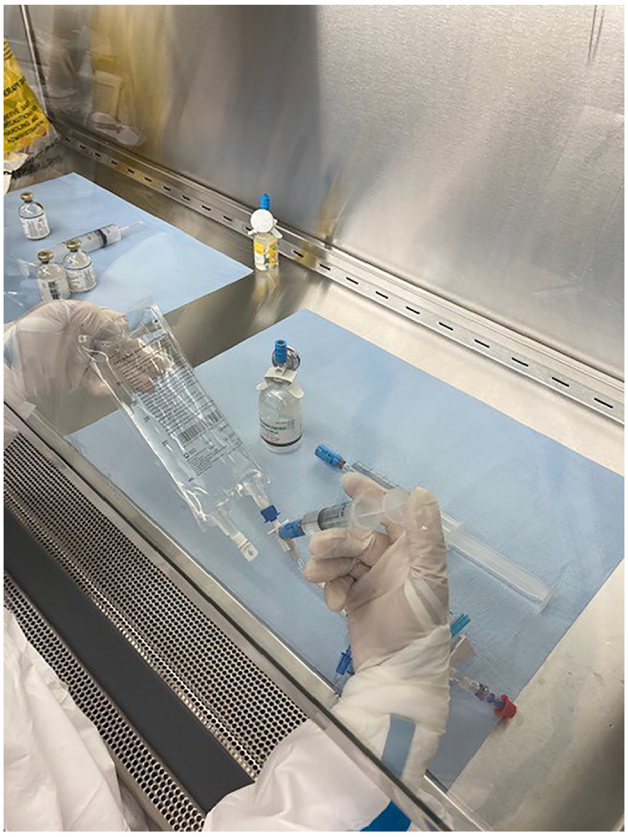

Figure 2: Compounding activities inside the BSC, prior to HD sampling activities.

The sampling was conducted by the facility's lead sterile compliance pharmacy technician.

In accordance with the vendor's direction for use of the surface wipe kits utilized for sample collection (ChemoGLOW™, Chapel Hill, NC), a square foot (929 cm^2) area was measured and marked for each sample location. A horizontal and vertical wipe sample were then taken from each area, after evenly distributing the wiping solution in the marked area. All samples were then recorded, placed inside a container provided by the surface wipe analysis kit vendor and sent to the vendor laboratory for analysis. All samples were identified indicating the sampling location, time/date of collection, and initials of personnel performing the sampling.

Reference testing: The samples to determine surface contamination of the workplace with HDs were stored at 4 °C, in accordance with the surface kit instructions for use (ChemoGLO, Durham, NC, USA). These samples were shipped to the ChemoGLO reference lab where they were stored at 4 °C until processed and analyzed. The samples were analyzed in accordance with previously published methods [27]. Briefly, the HD samples were extracted using an extraction solution, transferred to a Salivette tube with an insert, and centrifuged at 4,000 rpm for 10 min. A 200 µL aliquot of the resulting solution was removed from the bottom chamber of the tube, dried down and then reconstituted with 30 mL of mobile phase solution. A 200 µL solution containing internal standards (IS) was added to each swab as the internal standard.

The sample was then analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS), as previously described [28–32]. The analyzation of the samples was performed utilizing assays using an Agilent 6410 Triple Quadrupole with a concentration range for the sampled HDs linear 10–2,000 ng/mL per swab area.

The ChemoGLO sample kits, method of collection, transport, and analysis have demonstrated, when used in accordance with the IFU, to recover >90% of cyclophosphamide, ifosfamide, paclitaxel, docetaxel, 5-FU and methotrexate from a sample surface area [27]. The methods are aligned with the recommendations of recent publications, including extraction solution, wiping method, wiping materials, and instrumental considerations [33].

Results

Surface wipe kits analyzed from the initial (0 month), first follow up (3 month), and second follow up (6 month) all resulted in below the limit of detection (0.01 ng/cm^2), resulting in non-detectable surface contamination for all surface/HD combinations. The results are displayed in Table 2, below:

The number of preparations of the five HDs analyzed during the course of the evaluation are identified in Table 3, below:

Figure 3: HD sampling area of the nursing staging area.

Table 3: HD preparation frequency.

Hazardous drug	Number of preparations
Paclitaxel	205
Fluorouracil	169
Cyclophosphamide	89
Methotrexate	46
Doxorubicin	84

Discussion

Surface contamination remains a concern for hospital and pharmacy workers and a potential hazard to the health of these healthcare workers. As discussed with Connor et al. [2], surface contamination may still be present, creating an unnecessary risk to staff. Factors outside of the control of the hospital staff may contribute to the presence of surface contamination. For instance, spills that do not get noticed by hospital staff, or are under or not reported may contribute to the presence of HD vapor. Also, the presence of contamination may be a result of vial contamination, as reported in previous studies [34, 35]. The above factors may remain outside the immediate control of hospital staff and may warrant additional study to determine factors and strategies to mitigate or eliminate potential contamination sources.

Table 2: Initial, 3 month, and 6 month surface contamination wipe analysis (ng/cm^2).

Timepoint	Location	Paclitaxel	5-FU	Cyclophosphamide	Methotrexate	Doxorubicin
Initial	Biological safety cabinet hood	<0.01	<0.01	<0.01	<0.01	<0.01
	Pharmacy pass thru to nursing area	<0.01	<0.01	<0.01	<0.01	<0.01
	Nursing staging area	<0.01	<0.01	<0.01	<0.01	<0.01
	Main pharmacy pass thru	<0.01	<0.01	<0.01	<0.01	<0.01
	Main pharmacy counter in mixing room	<0.01	<0.01	<0.01	<0.01	<0.01
	Inpatient chemo bin nursing	<0.01	<0.01	<0.01	<0.01	<0.01
3 month follow up	Biological safety cabinet hood	<0.01	<0.01	<0.01	<0.01	<0.01
	Pharmacy pass thru to nursing area	<0.01	<0.01	<0.01	<0.01	<0.01
	Nursing staging area	<0.01	<0.01	<0.01	<0.01	<0.01
	Main pharmacy pass thru	<0.01	<0.01	<0.01	<0.01	<0.01
	Main pharmacy counter in mixing room	<0.01	<0.01	<0.01	<0.01	<0.01
	Inpatient chemo bin nursing	<0.01	<0.01	<0.01	<0.01	<0.01
6 month follow up	Biological safety cabinet hood	<0.01	<0.01	<0.01	<0.01	<0.01
	Pharmacy pass thru to nursing area	<0.01	<0.01	<0.01	<0.01	<0.01
	Nursing staging area	<0.01	<0.01	<0.01	<0.01	<0.01
	Main pharmacy pass thru	<0.01	<0.01	<0.01	<0.01	<0.01
	Main pharmacy counter in mixing room	<0.01	<0.01	<0.01	<0.01	<0.01
	Inpatient chemo bin nursing	<0.01	<0.01	<0.01	<0.01	<0.01

This study supports the value of standardized cleaning procedures and the presence of a secondary engineering control, in the identity of a CSTD, to retain reduced environmental exposure of healthcare workers to HD surface contamination, based upon previously identified threshold values [2]. It should be noted that the choice of cleaning solution may not be the primary determinant in the effectiveness in its ability to decontaminate HD spills or residue. As mentioned previously, research has indicated that additional factors, besides the solution, may be substantial contributors to the effectiveness including mechanical action, which may physically remove the HD and may be affected by the porosity or makeup of the material used to apply the solution [18].

Surface contamination evaluation by surface wipe analysis remains an established technique to identify the presence of HD and potential exposure of healthcare workers, especially those involved in the preparation, compounding, and administration of HD. Although this is an established technique, it should be noted that there are limitations involved in the evaluation. HD stability, and the breakdown of the HD molecules varies, dependent upon the HD, and may have the consequence of resulting in false negative reporting results due to the nature of the HD and because of the lack of real time sampling ability. Another limitation is the variable of the surface being sampled, information may be needed to determine the extent of factors such as: porosity, material makeup, and alignment, as these factors have all been demonstrated to have an effect upon recovery rate [36] and may have contributed to the consistency of sampling results and sample capture rate.

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