

# Development and evaluation of a novel product to remove surface contamination of hazardous drugs



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# Development and evaluation of a novel product to remove surface contamination of hazardous drugs

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## Abstract

**Background:** Even while following best practices, surface exposures of hazardous drugs (HDs) are high and numerous. Thus, it is important to develop new products to reduce the surface contamination of HDs. Hazardous Drug Clean (HDClean™) was developed to decontaminate and remove HDs from various types of surfaces and overcome the problems associated with other cleaning products.

**Methods:** HDClean was evaluated to remove mock surface exposures of HDs (docetaxel, paclitaxel, ifosfamide, cyclophosphamide, 5-FU, and cisplatin) from various types of surfaces. In two separate cancer centers, studies were performed to evaluate HDClean in reducing surface contamination of HDs in the pharmacy departments where no closed system transfer device (CSTD) was used. In a third cancer center, studies were performed comparing the effectiveness of a CSTD + Surface Safe compared with CSTD + HDClean to remove HDs.

**Results:** HDClean was able to completely remove mock exposures of a wide range of HDs from various surfaces (4 and 8 sq ft areas). Daily use of HDClean was equal to or more effective in reducing surface contamination of HDs in two pharmacies compared with a CSTD. HDClean was significantly more effective in removing HDs, especially cisplatin, compared with Surface Safe and does not have the problems associated with decontamination solutions that contain sodium hypochlorite.

**Conclusion:** These studies support HDClean as an effective decontaminating product, that HDClean is more effective than Surface Safe in removing HDs and is equal to or more effective than CSTD in controlling HD surface exposures.

## Keywords

Hazardous drugs, surface contamination, decontamination, cleaning, HDClean

## Introduction

Medications play an important role in treating and managing various disease states. With their broad use, numerous providers, patients, and family members could have contact with these drugs. For disease states such as organ transplantation, autoimmune diseases, cancer, and infections, the specific medications used for management have been demonstrated to exhibit specific concerns for the health care worker.<sup>1</sup> Studies over the past five decades show employees handling hazardous drugs (HDs) are at increased risk for drug-related toxicities.<sup>2–11</sup> HDs may exert undesirable effects on employees through direct skin contact or systemic

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absorption due to the inhalation of aerosols, hand-to-mouth transfer, or accidental needle sticks.

Even with appropriate aseptic technique, work area surfaces may easily become contaminated with HDs leading to undesirable occupational exposure.<sup>10</sup> One study published in 1979 described the occupational adverse effects of handling HDs. Researchers found significantly increased mutagenicity of urine bacteria concentrates in nurses handling antineoplastic agents when compared to controls.<sup>12</sup> In a more recent cross-sectional study of 68 exposed health care workers and 53 controls at three US-based cancer centers, measurable concentrations of antineoplastic agents were detected in urine samples from health care workers after chemotherapy preparation.<sup>13</sup>

At the base of occupational exposure prevention methods for HDs are engineering controls, proper procedures, and personal protective equipment (PPE). Besides proper aseptic technique training, one must also utilize workplace controls to minimize exposure to HDs. Primary engineering controls, a Compounding Aseptic Containment Isolator (CACI) or a Class II Biological Safety Cabinet (BSC) Type B2, should be used for all compounding activities, being physically separated from non-hazardous compounding areas.<sup>14</sup> PPE is intended to minimize exposure to health care workers by providing a barrier between a worker and the hazardous compound. These include appropriately rated and chemotherapy-tested gloves, gowns, and face-masks when necessary. In addition, many organizations have implemented closed system transfer devices (CSTDs). Since the first device became available in 1997 (PhaSeal<sup>®</sup>), there has been a steady rise in utilization within the health care setting. CSTDs are drug-transferring devices mechanically prohibiting the transfer of environmental contaminants into the sterile system and the escape of hazardous drugs or vapors outside the system.<sup>15</sup> United States Pharmacopeia (USP) recommends the use of CSTDs, primarily to decrease the exposure to HDs.<sup>16</sup> However, studies suggest that an additional source of HD surface contamination is attributed to exposures of HDs on the outsides of vials generated during the manufacturing process.<sup>17,18</sup>

Healthcare workers who are exposed to HD as part of their work practice should take precaution to eliminate or reduce exposure as much as possible. Nurses and pharmacists who prepare and/or administer these hazardous drugs are the two occupational groups who have the highest exposure potential to hazardous drugs. Studies designed to detect chemotherapy surface contamination show that 80–90% of nursing and pharmacy related sites evaluated for HD surface residue have at least one area of detectable hazardous drug surface contamination, even while following best practices.<sup>19–28</sup> Because of this, it is important to evaluate

and develop further methods to reduce and remove the surface contamination of HD.

The draft of USP800 (May 2015) includes recommendations and best practices on ways to prevent and to remove surface contamination of HDs.<sup>29</sup> Potential methods of removal of HDs include deactivation, decontamination and cleaning. Deactivation renders a compound inert or inactive. Decontamination occurs by physically removing HD residue from non-disposable surfaces and transferring it to absorbent, disposable materials (e.g. wipes, pads, or towels) appropriate to the area being cleaned. All disposable materials must be discarded as contaminated HD waste. As related to deactivation, chemical deactivation of HD residue is preferred, but no single process has been found to deactivate all currently available HDs. Studies have examined oxidizing agents that have varying results. Moreover, some potential deactivators have produced byproducts that are as hazardous as the original drug. Other deactivators have respiratory effects or result in caustic damage to surfaces. For example, sodium hypochlorite is corrosive to stainless steel surfaces if left untreated; therefore, sodium hypochlorite must be neutralized with sodium thiosulfate or followed by use of a germicidal detergent. Cleaning is a process that results in the removal of contaminants (e.g. HD residue) from objects and surfaces using water, detergents, surfactants, solvents, and/or other chemicals. A multi-component system to remove surface contamination of HDs is theoretically more efficient than a single component or method system because of the diverse nature of HDs. For example, a product that combines the ability to decontaminate and clean may be most effective. With the availability of assays to measure HD surface contamination, USP800 recommends surface wipe sampling to document the effectiveness of any agent used remove HD residue from work surfaces.

Surface Safe is a towelette system containing sodium hypochlorite that is designed to decontaminate and deactivate surface contamination of some HDs.<sup>30</sup> However, studies evaluating Surface Safe did not evaluate or report the removal of HDs or evaluate exposures of HDs on surfaces. Moreover, the studies were only performed in test tubes and only evaluated if the form of the 3 HDs with very similar chemical characteristics was potentially changed by evaluating binding to DNA. Thus, formal studies evaluating the ability of this product to remove a wide range of HDs from surfaces have not been reported. In addition, Surface Safe is associated with a very strong odor due to the sodium hypochlorite, leaves an oil-like residue that must be removed with the use of an additional cleaning product, and is designed to work on a relatively small area (2 sq ft area). Moreover, the sodium hypochlorite in Surface Safe is corrosive to stainless-steel surfaces.

Hazardous Drug Clean (HDClean™) was developed to address the need for a product that can decontaminate, clean and remove HDs with highly variable chemical characteristics from various types of surfaces. In addition, HDClean is a two-step towelette cleaning product that was designed to remove HDs from surfaces and to overcome the problems associated with Surface Safe (e.g. odor, corrosiveness, need for second cleaning product, use of a small area). Here, we report a series of research and development studies and testing in three separate cancer centers that evaluated the ability of HDClean to remove surface contamination of a series of HD with vastly different chemical characteristics and solubilities. The evaluation of HDClean was performed in pharmacies and nursing units. Analytical chemistry methods also were used to accurately measure the concentrations of HDs on surfaces as outlined in the draft of USP800 (May 2015).<sup>29</sup>

## Methods

### Evaluation of HDClean on mock surface contaminations

**Objectives.** The goal of this experimentation was to evaluate the effectiveness of HDClean in removing surface contamination of HDs from a stainless steel surface. HDClean was used to clean 4 sq ft (2 ft × 2 ft) and 8 sq ft (4 ft × 2 ft) areas. The HDClean dual component towelettes were used to clean all areas using the standard cleaning procedure. HDClean towelette #1 (quaternary ammonium based solution) was used to clean each area first and then HDClean towelette #2 (isopropyl alcohol-based solution) was used to clean each area. This procedure was repeated a second time on each contaminated area.

**Study design.** Docetaxel, paclitaxel, ifosfamide, cyclophosphamide, and 5-fluorouracil (5-FU) were added to a single solution in 37.5:37.5:25 methanol:acetonitrile:water to give a final nominal concentration of 500 ng/mL of each drug. Cisplatin was added to a separate solution of 2% nitric acid to give a 500 ng/mL solution. Surfaces were “contaminated” with the drug solutions of 500 ng/mL to give a nominal amount of 500 ng of each drug per square foot. All solutions were allowed to dry completely before testing. These drugs were selected as they represent some of the most frequently administered anticancer agents and have a wide variety of chemical characteristics (e.g. structures, solubilities).

**Cleaning and sampling procedures.** HDClean was used to clean 4 and 8 sq ft areas using the standard methods described above. After cleaning, each area was then

sampled ( $n=4$  separate 1 ft × 1 ft areas) using ChemoGLO (Chapel Hill, NC) wipe kits to extract all six drugs from the surface. Surface areas that were not treated with HDClean were also sampled ( $n=4$  separate 1 ft × 1 ft areas) as baseline measurements of surface exposures of HD. ChemoGLO wipe kits and analytical methods were used to evaluate the surface exposure of docetaxel, paclitaxel, 5-FU, ifosfamide, cyclophosphamide and cisplatin as described below in detail.

### Evaluation of HDClean on different types of surfaces

**Objectives and study design.** This investigation was designed to evaluate the effectiveness of HDClean at removing HD contamination on different types of surfaces over the course of one week. Six different areas were selected based on frequency of use and potential for contamination or exposure in pharmacies and nursing units. A summary of the surface areas and materials that were evaluated is given in Table 1. These studies were performed in a separate hospital than described below for Cancer Centers #1, #2, and #3.

**Study design, cleaning and sampling procedures.** A section of each area measuring 4 sq ft (2 ft × 2 ft) was delineated. This large section was then subdivided into four 1 sq ft sections. Before cleaning, initial drug contamination was evaluated using ChemoGLO wipe kits to sample 1 square foot of each area. HDClean wipes were used as directed to clean the six selected surfaces daily at end of the day. Surface contamination of HD was evaluated at end of the second and fifth day of cleaning with HDClean. ChemoGLO wipe kits were used to evaluate the surface exposure of docetaxel, paclitaxel, 5-FU, ifosfamide, cyclophosphamide and platinum analogues (e.g. cisplatin, carboplatin, and oxaliplatin) as outlined below.

### Evaluation of HDClean in pharmacy at cancer centers #1 and #2 not using a CSTD

**Objective.** The primary objective of this study was to evaluate the effectiveness of HDClean in reducing

**Table 1.** Summary of surface area and material evaluated.

Surface area	Material
BSC	Stainless steel
Floor under BSC	Waxed tile
Table top	Phenolic resin
Floor under preparation area	Waxed tile
Computer keyboard	Plastic; phenolic resin

surface contamination of HDs in the pharmacy departments of two separate cancer centers where no CSTD or robot was used to prepare doses of chemotherapy.

**Study design, cleaning, and sampling procedures.** Chemo-therapy surface contamination was evaluated in both cancer centers before and after the use of HDClean. Six different locations in each cancer center were evaluated for surface contamination of docetaxel, paclitaxel, 5-FU, cyclophosphamide, ifosfamide, methotrexate and platinum analogues. Surface samples were obtained at baseline (prior to cleaning with HDClean). HDClean was used twice per day (in the morning and afternoon) in all studies. In study 1, wipe studies were performed on day 5 of weeks 1 and 2 after using HDClean in the morning, preparing chemotherapy during the day but before performing the second HDClean cleaning procedure in the afternoon (first HDClean cleaning procedure → preparing chemotherapy → surface wipe study → second HDClean cleaning procedure). In study 2, the wipe studies were performed on day 5 of week 1 after preparation of chemotherapy and immediately following the second daily cleaning procedure using HDClean (first HDClean cleaning procedure → preparing chemotherapy → second HDClean cleaning procedure → surface wipe study). Surface contamination of HD was evaluated using ChemoGLO wipe kits. The wipe Kit samples were analyzed for docetaxel, paclitaxel, 5-FU, cyclophosphamide, ifosfamide, methotrexate and platinum analogues at the ChemoGLO reference lab as described below.

### **Evaluation of HDClean in pharmacy and nursing unit at cancer center #3**

**Objectives.** The studies outlined above evaluated HDClean in pharmacy departments that prepare chemotherapy. However, there is also the potential for high exposures of HDs in nursing units where chemotherapy is administered to patients. Thus, this study evaluated the effectiveness of HDClean to reduce exposures of HD on surfaces in a pharmacy and a nursing unit in a separate cancer center from the studies performed in cancer centers #1 and #2. In addition, the effectiveness of HDClean in removing surface contamination of HDs was compared to Surface Safe.

**Study design, cleaning and sampling procedures.** Studies were performed to evaluate the ability of HDClean to remove chemotherapeutic agents from surfaces in the pharmacy department and nursing unit in a cancer center. The center utilized all best practices, including a CSTD and Surface Safe®, a commercially available decontamination agent. Surface Safe® was used as per

manufacturer's recommendations. Six surface wipe studies were conducted using the ChemoGLO wipe kit, four in pharmacy and two in nursing unit. Surface wipe studies were performed at baseline when Surface Safe + CSTD were used and after changing the cleaning product to HDClean (HDClean + CSTD). HDClean was used daily for two weeks. The ChemoGLO wipe Kit samples were analyzed for docetaxel, paclitaxel, 5-FU, cyclophosphamide, ifosfamide, and methotrexate at the ChemoGLO reference lab as described below.

### **Surface sampling wipe kits and analytical assay**

ChemoGLO Wipe Kits™ (Chapel Hill, NC) quantifies amounts of contaminants of the antineoplastic agents 5-FU, ifosfamide, cyclophosphamide, methotrexate, docetaxel, paclitaxel and platinum analogues (e.g. cisplatin, carboplatin and oxaliplatin) on surfaces. Each kit contains enough materials to conduct six wipes. To ensure proper technique in collecting the samples, a training video and written instructions were provided by the reference lab and in turn reviewed by the research team that collected the samples. Standardized surfaces of approximately 144 in<sup>2</sup> (12 × 12 inches) were sampled with two wipes each, one vertical wipe and one horizontal wipe. Prior to wiping, each swab was moistened with 2 mL of a solution containing isopropyl alcohol. The wipe procedure is able to recover >90% of cyclophosphamide, ifosfamide, paclitaxel, docetaxel, 5-FU and methotrexate from a 12 × 12 inch surface.

Samples were stored at 4°C on site until they were shipped to the ChemoGLO reference lab where they were stored at 4°C until processed and analyzed. A 200 µL solution containing internal standards (IS) [cyclophosphamide-d4 (CPM-d4) for cyclophosphamide; antipyrine (APR) for ifosfamide; paclitaxel-d5 for paclitaxel; docetaxel-d9 for docetaxel; 5-FU-<sup>13</sup>C,<sup>-15</sup>N<sub>2</sub> for 5-FU; methotrexate-d3 for methotrexate] was added to each swab as the internal standard. The drugs and IS were extracted from the wipe swab using 2 mL of an extraction solution. The contents (swab and solution) were transferred to a Salivette tube with an insert and centrifuged at 4000 rpm for 10 min. A 200 µL aliquot of the resulting solution was removed from the bottom chamber of the Salivette tube, dried down and then reconstituted with 30 µL of mobile phase solution. The sample was then analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays using an Agilent 6410 Triple Quadrupole as previously described.<sup>31-35</sup> The range of cyclophosphamide, ifosfamide, paclitaxel, docetaxel, 5-FU and methotrexate concentrations measured by the assays was linear 10 to 2000 ng/mL per swab area. The

**Table 2.** Mean  $\pm$  SD concentrations (ng/sq ft) of six antineoplastic drugs on surfaces before and after cleaning procedures in the mock surface contamination studies.

Experiment		Docetaxel	Paclitaxel	5-FU	Ifosfamide	Cyclophosphamide	Cisplatin
Baseline no cleaning [1 ft $\times$ 1 ft = 1 sq ft area] ( <i>n</i> = 7) <sup>a</sup>	Drug Amt (ng/sq ft)	525.5 $\pm$ 150.0	562.6 $\pm$ 68.2	596.8 $\pm$ 25.5	521.2 $\pm$ 75.1	486.4 $\pm$ 31.1	479.5 $\pm$ 80.3
	No. of detectable samples	<i>n</i> = 4	<i>n</i> = 4	<i>n</i> = 4	<i>n</i> = 4	<i>n</i> = 4	<i>n</i> = 4
HDClean [2 ft $\times$ 2 ft = 4 sq ft area] ( <i>n</i> = 10) <sup>a</sup>	Drug amount (ng/sq ft)	ND	ND	ND	ND	ND	ND
	No. of detectable samples	<i>n</i> = 0	<i>n</i> = 0	<i>n</i> = 0	<i>n</i> = 0	<i>n</i> = 0	<i>n</i> = 0
HDClean double area [2 ft $\times$ 4 ft = 8 sq ft area] ( <i>n</i> = 12) <sup>a</sup>	Drug amount (ng/sq ft)	ND	ND	7.3 $\pm$ 13.8	17.6 $\pm$ 31.9	ND	187.5 $\pm$ 73.2
	No. of detectable samples	<i>n</i> = 0	<i>n</i> = 0	<i>n</i> = 4	<i>n</i> = 3	<i>n</i> = 0	<i>n</i> = 12

ND = non-detectable drug exposure.

<sup>a</sup>The number listed represents the number of replicate areas sampled for surface contamination at base (*n* = 7), HDClean 4 sq ft area (*n* = 10) and HDClean 8 sq ft area (*n* = 12). The number of replicate sampling areas was increased from baseline to HDClean 4 sq ft area to HDClean 8 sq ft area in order to get a better representation of the exposures over the entire areas.

correlation coefficients for three successive duplicate standard curves were all  $>0.99$ . The accuracy for each drug at the lower limit of quantitation (LLQ) and for the standard concentrations were  $<20\%$  and  $<15\%$ , respectively, of the theoretical values. Intra-assay and inter-assay precision was  $<10\%$  for all drugs. As the volume of solutions added to each swab is maintained constant, the results are reported as ng/sq ft. The results of the two swabs used to wipe each area (1 swab used to wipe horizontal and 1 swab used to wipe vertical) are then added together to give a final exposure result for each sample area in ng/sq ft.

The same swab used for the surface sampling of the drugs listed above underwent further sample processing to measure platinum (Pt) analogues via Inductively Coupled Plasma Mass Spectrometry (ICP-MS).<sup>36,37</sup> The swab was processed as previously described.<sup>36,37</sup> Briefly, the swab is processed with 1 mL of 5% of nitric acid that contains 20 ppb of Iridium (Ir) as the internal standard (IS), followed by 1 mL of water. All washes from each swab are pooled to produce 2 mL of reconstituted sample in 2.5% nitric acid in water. Analysis of the samples is performed using a Nexion 300 D ICP-MS, in which elemental metals are ionized through heating and then drawn into a mass spectrometer for detection based on mass-to-charge ratios (*m/z*). Pt concentrations measured by the assays were linear

10–1,000 ng/mL per swab area. The accuracy for each drug at the lower limit of quantitation (LLQ) and for the standard concentrations was  $<20\%$  and  $<15\%$ , respectively, of the theoretical values. Intra-assay and inter-assay precision were  $<10\%$  for all drugs.

## Results

### Evaluation of HDClean on mock surface contaminations

HDClean was evaluated to remove the surface contamination of docetaxel, paclitaxel, 5-FU, ifosfamide, cyclophosphamide, and cisplatin that was added to the surfaces to achieve a final exposure of 500 ng/sq ft on 4 sq ft and 8 sq ft areas. The results of this study are summarized in Table 2. The baseline (prior to cleaning) surface exposure of each drug was approximately 500 ng/sq ft. The use of HDClean on the 4 sq ft area resulted in non-detectable concentrations of all drugs in all 10 surface areas. The use of HDClean on the 8 sq ft area resulted in non-detectable concentrations of docetaxel, paclitaxel and cyclophosphamide in all 12 surface areas. HDClean also achieved pronounced reductions in 5-FU and ifosfamide exposures on the 8 sq ft area. The mean % reduction in 5-FU was 98.8% with detectable drug in only 4 of the 12 surface areas.

**Table 3.** Summary of Docetaxel surface exposures at baseline and after HDClean.

Surface area cleaned		Docetaxel exposure at baseline (prior to cleaning)	Docetaxel exposures after 2 daily cleanings with HDClean	Docetaxel exposures after 5 daily cleanings with HDClean
BSC	ng/sq ft (% reduction)	34.7	ND (100%)	ND (100%)
Floor under BSC	ng/sq ft (% reduction)	80.5	37.6 (53.3%)	ND (100%)
Table top	ng/sq ft (% reduction)	>4000.0	3848.6 (3.8%)	411.9 (89.7%)
Floor under preparation area	ng/sq ft (% reduction)	310.5	88.6 (71.5%)	58.0 (81.3%)
Computer keyboard	ng/sq ft (% reduction)	14.1	ND (100%)	ND (100%)

ND = non-detectable drug exposure.

**Table 4.** Summary of paclitaxel surface exposures at baseline and after HDClean.

Surface area cleaned		Paclitaxel exposure at baseline (prior to cleaning)	Paclitaxel exposures after two daily cleanings	Paclitaxel exposures after five daily cleanings
BSC	ng/sq ft (% reduction)	19.9	ND (100%)	ND (100%)
Floor under BSC	ng/sq ft (% reduction)	ND	ND	ND
Table Top	ng/sq ft (% reduction)	>4000.0	311.4 (92.2%)	73.3 (98.2%)
Floor under preparation area	ng/sq ft (% reduction)	372.9	31.4 (91.6%)	30.2 (81.3%)
Computer keyboard	ng/sq ft (% reduction)	22.9	ND (100%)	ND (100%)

ND = non-detectable drug exposure.

The mean % reduction in ifosfamide was 96.6% with detectable drug in only 3 of 12 surface areas. In addition, HDClean achieved pronounced reductions in cisplatin in all 12 sample areas evaluated with mean percentage reduction of 60.9%. In summary, HDClean was equally effective in removing all drugs from the 4 sq ft and 8 sq ft areas. The only exception was for cisplatin where HDClean resulted in a 100% and 60% reductions in the 4 sq ft and 8 sq ft areas, respectively.

### Evaluation of HDClean on different types of surfaces

The ability of HDClean to remove HDs from different types of surfaces was evaluated after 2 and 5 daily cleanings. The types of surfaces evaluated are summarized in Table 1 and included BSC, floors, bench tops and computer key boards. The summary of surface exposures docetaxel, paclitaxel, 5-FU and cisplatin at baseline and after 2 and 5 daily cleanings are included in Tables 3–6. The baseline exposures of the drugs were

highly variable on the different types of surfaces. Daily use of HDClean after two days and especially five days resulted in pronounced reductions of all drugs on all types of surfaces with most surfaces have non-detectable exposures of HD after use of HDClean. Ifosfamide was only detectable at baseline on table top (141.3 ng/sq ft) and floor under preparation (19.6 ng/sq ft) area. Both locations were non-detectable after two daily cleanings using HDClean. Cyclophosphamide was only detectable at baseline in the biological safety cabinet (BSC) (620.1 ng/sq ft). After two and five daily cleanings with HDClean, the exposures of cyclophosphamide were 197.6 ng/sq ft (68.2% reduction) and non-detectable (ND) (100.0% reduction). In most cases, all of the drugs were non-detectable on all surfaces after use of HDClean for five consecutive days.

### Evaluation of HDClean in pharmacy at cancer center #1 and #2 not using a CSTD

This study evaluated the surface exposure of chemotherapy in two separate cancer centers that were not

**Table 5.** Summary of 5-FU surface exposures at baseline and after HDClean.

Surface area cleaned		5-FU exposure at baseline (prior to cleaning)	5-FU exposures after two daily cleanings	5-FU exposures after five daily cleanings
BSC	ng/sq ft (% reduction)	172.9	47.9 (72.1%)	ND (100%)
Floor under BSC	ng/sq ft (% reduction)	2285.0	266.2 (88.4%)	247.8 (89.16%)
Table Top	ng/sq ft (% reduction)	>4000.0	475.5 (88.1%)	163.1 (95.9%)
Floor under preparation area	ng/sq ft (% reduction)	>4000.0	226.4(94.3%)	186.3 (95.3%)
Computer keyboard	ng/sq ft (% reduction)	384.6	ND (100%)	ND (100%)

ND = non-detectable drug exposure.

**Table 6.** Summary of cisplatin surface exposures at baseline and after HDClean.

Surface area cleaned		Cisplatin exposure at baseline (prior to cleaning)	Cisplatin exposures after two daily cleanings	Cisplatin exposures after five daily cleanings
BSC	ng/sq ft (% reduction)	20.1	ND (100%)	ND (100%)
Floor under BSC	ng/sq ft (% reduction)	22.9	ND (100%)	ND (100%)
Table Top	ng/sq ft (% reduction)	423.9	16.6 (96.1%)	ND (100%)
Floor under preparation area	ng/sq ft (% reduction)	34.9	ND (100%)	ND (100%)
Computer keyboard	ng/sq ft (% reduction)	24.4	ND (100%)	ND (100%)

ND = non-detectable drug exposure.

using a CSTD. In study 1, wipe studies were performed on day 5 of weeks 1 and 2 after using HDClean in the morning, preparing chemotherapy during the day but before performing the second HDClean cleaning procedure in the afternoon on that day. In study 2, the wipe studies were performed after preparation of chemotherapy and immediately following the second daily cleaning procedure using HDClean.

A summary of surface exposures of the HDs at baseline and after use of HDClean in studies 1 and 2 are presented in Tables 7 (cancer center #1) and 8 (cancer center #2). In study 1, the concentrations of most drugs at most locations at 1 and 2 weeks after starting HDClean achieved pronounced reductions in exposures as compared to baseline even though the wipe studies were performed after the preparation of chemotherapy on that day but before the second HDClean procedure.

In study 2, the surface exposure of all drugs on all surfaces were non-detectable except for 5-FU in one location in cancer center #2. Thus, the total percentage of detectable exposures of drugs in study 2 was only 1.1% [1 out of 84 (7 drugs in 12 locations) potential drug exposures]. Based on the results of study 2, the few high or increased concentrations of drugs in study 1 on weeks 1 and 2 compared to baseline are most likely due to surface contamination associated with

preparing chemotherapy that day as the wipe studies were performed prior use of HDClean. These results highlight the potential of HD accumulation on a daily basis.

### *Evaluation of HDClean in pharmacy and nursing unit at cancer center #3*

Surface exposures of chemotherapy were measured in both pharmacy and nursing units for five drugs in a total of six locations for a total of 30 sample results. These studies were performed in a separate cancer center from sites #1 and #2. The baseline wipes were performed after use of CSTD and Surface Safe. The cancer center then switched to the use of HDClean to clean surfaces and wipe studies. Wipe studies after the implementation of HDClean were then performed in the same locations as the baseline studies.

Surface exposures of chemotherapeutic agents prior to and after the use of HDClean in the pharmacy and nursing units are presented in Table 9. In wipe studies prior to the use of HDClean, there were detectable exposures for four of the five drugs analyzed with drugs detectable in 8 of 30 samples (26.7%). In addition, paclitaxel and ifosfamide exposures were >600 ng/sq ft at baseline. The baseline results are especially important as the site was using a CSTD and the



**Table 7.** Surface exposure of chemotherapeutic agents at baseline and in studies 1 and 2 after use of HDclean in cancer center #1.

Study	Wipe ID	Location	Docetaxel exposure (ng/sq ft)	Paclitaxel exposure (ng/sq ft)	5-FU exposure (ng/sq ft)	Cyclophosphamide exposure (ng/sq ft)	Ifosfamide exposure (ng/sq ft)	Methotrexate exposure (ng/sq ft)	Platinum exposure (ng/sq ft)
Baseline	1	Hood tray	ND	>3578.6	2771.4	2,065.0	ND	ND	240.5
Baseline	2	Hood pass thru handle	ND	42.7	206.8	1,417.5	ND	ND	20.1
Baseline	3	Negative pressure room interior door handle	ND	ND	77.0	66.6	ND	ND	ND
Baseline	4	Ante room interior door handle	ND	ND	ND	ND	ND	ND	ND
Baseline	5	Nurses' station counter	ND	ND	32.4	ND	ND	ND	ND
Baseline	6	Exterior ante room door handle	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 1	1	Hood tray	365.9	56.9	2609.6	66.6	ND	ND	32.1
Study 1 Wk 1	2	Hood pass thru handle	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 1	3	Negative pressure room interior door handle	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 1	4	Ante room interior door handle	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 1	5	Nurses' station counter	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 1	6	Exterior ante room door	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 2	1	Hood tray	67.2	ND	145.2	ND	ND	ND	30.9
Study 1 Wk 2	2	Hood pass thru handle	336.8	ND	ND	ND	ND	ND	ND
Study 1 Wk 2	3	Negative pressure room interior door handle	47.9	ND	60.6	ND	ND	ND	ND
Study 1 Wk 2	4	Ante room interior door handle	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 2	5	Nurses' station counter	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 2	6	Exterior ante room door	ND	ND	ND	ND	ND	ND	ND
Study 2	1	Hood tray	ND	ND	ND	ND	ND	ND	ND
Study 2	2	Hood airlock exterior handle	ND	ND	ND	ND	ND	ND	ND
Study 2	3	Negative pressure room interior door handle	ND	ND	ND	ND	ND	ND	ND
Study 2	4	Ante room interior door handle	ND	ND	ND	ND	ND	ND	ND
Study 2	5	Nurses' station counter	ND	ND	ND	ND	ND	ND	ND
Study 2	6	Exterior ante room door handle	ND	ND	ND	ND	ND	ND	ND

ND = non-detectable.

**Table 8.** Surface exposure of chemotherapeutic agents at baseline and in studies 1 and 2 after use of HDClean in cancer center #2.

Study	Wipe ID	Location	Docetaxel exposure (ng/sq ft)	Paclitaxel exposure (ng/sq ft)	5-FU Exposure (ng/sq ft)	Cyclophos-phamide exposure (ng/sq ft)	Ifosfamide exposure (ng/sq ft)	Methotrexate exposure (ng/sq ft)	Platinum exposure (ng/sq ft)
Baseline	1	Biological safety cabinet	ND	ND	59.48	22.2	ND	ND	ND
Baseline	2	Negative pressure room floor	ND	82.6	1460.9	108.1	ND	ND	46.4
Baseline	3	Ante room counter	ND	ND	47.4	ND	ND	ND	ND
Baseline	4	Negative pressure room interior door handle	ND	ND	ND	ND	ND	ND	ND
Baseline	5	Nurses' station counter	ND	ND	ND	ND	ND	ND	ND
Baseline	6	Exterior ante room door handle	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 1	1	Biological safety cabinet	ND	ND	28.6	ND	ND	ND	ND
Study 1 Wk 1	2	Negative pressure room floor	ND	ND	92.3	32.5	ND	ND	ND
Study 1 Wk 1	3	Ante room counter	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 1	4	Negative pressure room interior door handle	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 1	5	Nurses' station counter	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 1	6	Exterior ante room door handle	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 2	1	Biological safety cabinet	ND	ND	20.7	186.3	ND	ND	ND
Study 1 Wk 2	2	Negative pressure room floor	ND	ND	54.3	489.3	ND	ND	ND
Study 1 Wk 2	3	Ante room counter	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 2	4	Negative pressure room interior door handle	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 2	5	Nurses' station counter	ND	ND	ND	ND	ND	ND	ND
Study 1 Wk 2	6	Exterior ante room door handle	ND	ND	ND	ND	ND	ND	ND
Study 2	1	Biological safety cabinet	ND	ND	ND	ND	ND	ND	ND
Study 2	2	Negative pressure room floor	ND	ND	108.4	ND	ND	ND	ND
Study 2	3	Ante room counter	ND	ND	ND	ND	ND	ND	ND
Study 2	4	Negative pressure room interior door handle	ND	ND	ND	ND	ND	ND	ND
Study 2	5	Nurses' station counter	ND	ND	ND	ND	ND	ND	ND
Study 2	6	Exterior ante room door handle	ND	ND	ND	ND	ND	ND	ND

ND = non-detectable.

**Table 9.** Surface exposures of chemotherapeutic agents prior to and after the use of HDClean in the pharmacy and nursing unit at cancer center #3.

Wipe ID	Location description	Department	Docetaxel exposure ng/ft <sup>2</sup> (ng/cm <sup>2</sup> )		HDClean	Paclitaxel exposure ng/ft <sup>2</sup> (ng/cm <sup>2</sup> )		HDClean	5-FU exposure ng/ft <sup>2</sup> (ng/cm <sup>2</sup> )		HDClean	Cyclophosphamide exposure ng/ft <sup>2</sup> (ng/cm <sup>2</sup> )		HDClean	Ifosfamide exposure ng/ft <sup>2</sup> (ng/cm <sup>2</sup> )		HDClean
			Pre <sup>a</sup>	Post <sup>b</sup>		Pre <sup>a</sup>	Post <sup>b</sup>		Pre <sup>a</sup>	Post <sup>b</sup>		Pre <sup>a</sup>	Post <sup>b</sup>		Pre <sup>a</sup>	Post <sup>b</sup>	
1	Pharmacy Hood 3 Middle	Pharmacy	15.7	ND	ND	630.8 (0.68)	ND	ND	135.1 (0.15)	ND	ND	ND	617.8	54.9			
2	Pharmacy Floor under Hood 3	Pharmacy	(0.02)	ND	ND	ND	ND	ND	ND	ND	ND	ND	(0.67)	(0.06)	ND	ND	ND
3	Pharmacy Pass Through Window	Pharmacy	ND	ND	ND	59.18 (0.06)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
4	Oncology Center – Pod 4 Counter	Pharmacy	ND	ND	ND	ND	ND	ND	31.98 (0.03)	ND	ND	ND	ND	ND	ND	ND	ND
5	Oncology Center – Pod 4 Chemo Bin	Nursing	ND	ND	ND	32.51 (0.04)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
6	Oncology Center – Pod 3 Counter	Infusion Area	ND	ND	ND	ND	ND	ND	11.28 (0.01)	ND	ND	ND	ND	ND	ND	ND	ND

<sup>a</sup>Pre HDClean samples were obtained after the use of a CSTD and cleaning with Surface Safe.

<sup>b</sup>Post HDClean samples were obtained after the use of CSTD and HDClean.

areas were treated with Surface Safe prior to performing the wipe studies.

After the cleaning agent was changed to HDClean, all exposures of all drugs in all locations were non-detectable except for an exposure of ifosfamide in one location in the BSC (1 out of 30 = 3.3%) ( $P < 0.05$ ). In addition, the exposure of ifosfamide at this location was reduced by 91.1% compared to baseline. The use of HDClean resulted in ~800% reduction in the number of locations with detectable drugs compared to the use of Surface Safe.

Additional studies were performed on areas with high use of cisplatin. The exposure of Pt at baseline prior to cleaning ( $n=4$ ) and after cleaning with Surface Safe ( $n=4$ ) were  $479.5 \pm 80.3$  ng/sq ft and  $503.5 \pm 160.3$  ng/sq ft, respectively. After cleaning with HDClean, the exposure of platinum (Pt) was non-detectable in all areas ( $n=4$ ).

## Discussion

This is the first series of research and development studies and testing in cancer centers that evaluated the ability of a cleaning product to remove surfaces contaminated with HDs with vastly different chemical characteristics and solubilities using analytical chemistry methods to accurately measure the concentrations of HDs on surfaces. HDClean was able to achieve pronounced reductions in all studies and complete decontamination in most studies that evaluated surface contamination of a wide range of HDs from a wide range of surfaces. In studies evaluating HDClean in two separate cancer centers that were not using a CSTD, daily use of HDClean was equal to or more effective in reducing surface contamination of HDs compared with a CSTD.<sup>19-26</sup> In addition, a third study in a separate cancer center was performed to evaluate the effectiveness of HDClean plus a CSTD compared with Surface Safe plus a CSTD. The results of this study demonstrated that HD residue remains on surfaces even when best practices are followed (e.g. use of CSTD). Moreover, the results of this study showed that HDClean is more effective in removing HDs from surfaces than Surface Safe and HDClean does not have the problems associated with Surface Safe (e.g. strong odor, corrosive to stainless steel).<sup>30</sup> In summary, the results of these studies fully support HDClean as an effective decontaminating and cleaning product for HDs based on the requirements outlined in the draft of USP800. Moreover, these are the first such studies published for any related product used to remove HD from surfaces.

HDClean was evaluated to remove the surface contamination of docetaxel, paclitaxel, 5-FU, ifosfamide, cyclophosphamide, and cisplatin that were added

to 4 sq ft and 8 sq ft surface areas. The use of HDClean on the 4 sq ft area resulted in non-detectable concentrations of all drugs in all surface areas. The use of HDClean on the 8 sq ft area resulted in non-detectable concentrations of docetaxel, paclitaxel and cyclophosphamide in all surface areas and pronounced reductions in 5-FU and ifosfamide exposures. Thus, HDClean was equally effective in removing all drugs from the 4 and 8 sq ft areas with the exception of cisplatin where HDClean resulted in 100% and 60% reductions in the 4 sq ft and 8 sq ft areas, respectively. The results of this study show that HDClean is effective in decontaminating and cleaning a wide variety of HD from surfaces.

A separate study was also performed to evaluate the ability of HDClean to remove drug contaminations from various types of surfaces. In this study, daily use of HDClean after two days and especially five days resulted in pronounced reductions of all HD on all types of surfaces. In most cases, all of the drugs were non-detectable on all surfaces after use of HDClean for five consecutive days. This study showed that HDClean is effective in removing HDs from a wide range of surfaces that are commonly present in pharmacies and nursing units.

To evaluate the effectiveness of HDClean alone in actual pharmacies, it was tested under two different conditions in two cancer centers that did not use a CSTD. In study 1, the concentrations of most drugs at most locations after cleaning with HDClean were significantly reduced as compared to baseline even though the wipe studies were performed after the preparation of chemotherapy on that day but before the second HDClean procedure. In study 2, the surface exposure of all drugs on all surfaces were non-detectable except for 5-FU in 1 location in cancer center #2 (detectable exposures in only 1.1% of locations) when HDClean was used to clean the surfaces at the end of preparing chemotherapy. These results of studies 1 and 2 highlight the need to use HDClean daily and especially at the end of the preparation of chemotherapy in order to remove all surface contamination associated with preparing chemotherapy that day. Moreover, the results of these studies suggest that HDClean is equal or more effective in reducing surface contamination of HDs compared with a CSTD.<sup>19-28</sup>

A third study in a cancer center was performed to evaluate the effectiveness of HDClean plus a CSTD compared with Surface Safe plus a CSTD. These results of this study demonstrated that HD residue remains on surfaces even when all best practices are followed (e.g. use of CSTD). As per the prior studies, HDClean was able to fully remove drug exposures from surfaces contaminated with 5-FU, cyclophosphamide, docetaxel, and paclitaxel, and reduce the exposure of ifosfamide

by >90%. Moreover, our results show that HDClean is more effective in removing a wide variety of HDs, especially platinum analogues, from various surfaces than Surface Safe.

## Conclusion

HDClean is a multi-component system that fully addresses the guidelines outlined in USP800 for a product that can decontaminate and remove HDs from surfaces and overcomes the problems associated with sodium hypochlorite or bleach-like products. Based on this series of research and development studies, studies in cancer centers, and the broad range of chemical and solubility characteristics of the drugs tested, the results suggest that HDClean can be used to successfully remove a wide variety of HDs from surfaces in hospitals, pharmacies, nursing units and laboratories or any other place where HDs are present. Moreover, the results of our studies suggest that HDClean is more effective than Surface Safe in removing HDs, especially platinum analogues, and equal to or more effective than CSTD in controlling HD surface contamination.<sup>19–22,30</sup> This study suggests that Pt analogues are much harder to remove from surfaces than other agents.

Potential limitations of this study include lack of evaluation of HDClean to remove surface exposures of biological agents (e.g. proteins and antibodies) and after acute chemotherapy spills. Additional studies are needed to address these types of exposures. However, the solutions used in HDClean are able to denature the types of proteins used in biological agents. For acute chemotherapy spills, it may be most appropriate to use existing methods to remove the chemotherapy and then use HDClean to clean the residual drug exposure. Additional studies are required to evaluate the factors associated with causing surface exposures, removing surface exposures, especially Pt agents, use of HDClean over larger surface areas, and to document potential safe levels of exposure.

## References

- Centers for Disease Control and Prevention. Proposed additions and deletions to the NIOSH Hazardous Drug List 2014. 2014.
- Skov T, Maarup B, Olsen J, et al. Leukaemia and reproductive outcome among nurses handling antineoplastic drugs. *Br J Ind Med* 1992; 49: 855–861.
- Levin LI, Holly EA and Seward JP. Bladder cancer in a 39-year-old female pharmacist. *J Natl Cancer Inst* 1993; 85: 1089–1091.
- McAbee RR, Gallucci BJ and Checkoway H. Adverse reproductive outcomes and occupational exposures among nurses: an investigation of multiple hazardous exposures. *AAOHN J* 1993; 41: 110–119.
- Valanis BG, Vollmer WM, Labuhn KT, et al. Association of antineoplastic drug handling with acute adverse effects in pharmacy personnel. *Am J Hosp Pharm* 1993; 50: 455–462.
- Valanis BG, Vollmer WM, Labuhn KT, et al. Acute symptoms associated with antineoplastic drug handling among nurses. *Cancer Nurs* 1993; 16: 288–295.
- Valanis B, Vollmer WM and Steele P. Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. *J Occup Environ Med* 1999; 41: 632–638.
- Lorente C, Cordier S, Bergeret A, et al. Maternal occupational risk factors for oral clefts. Occupational Exposure and Congenital Malformation Working Group. *Scand J Work Environ Health* 2000; 26: 137–145.
- Fransman W, Roeleveld N, Peelen S, et al. Nurses with dermal exposure to antineoplastic drugs: Reproductive outcomes. *Epidemiology* 2007; 18: 112–119.
- McDiarmid MA, Oliver MS, Roth TS, et al. Chromosome 5 and 7 abnormalities in oncology personnel handling anticancer drugs. *J Occup Environ Med* 2010; 52: 1028–1034.
- Xie J, Wang J, Li H, et al. Epidemiological study of effect of occupational exposure to antineoplastic drugs on reproductive outcome in nurses. *Cin J Ind Hyg Occup Dis* 2001; 19(2): 87–90.
- Nguyen TV, Theiss JC and Matney TS. Exposure of pharmacy personnel to mutagenic antineoplastic drugs. *Cancer Res* 1982; 42: 4792–4796.
- Connor TH, DeBord DG, Pretty JR, et al. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. *J Occup Environ Med* 2010; 52: 1019–1027.
- American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990; 47: 1033–1049.
- National Institute for Occupational Safety and Health. *Preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings*. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 2004.
- US Pharmacopeia U. *Guidebook to pharmaceutical compounding: sterile preparations*. Rockville, MD: United States Pharmacopeia, 2008.
- Schierl R, Herwig A, Pfaller A, et al. Surface contamination of antineoplastic drug vials: comparison of unprotected and protected vials. *Am J Health Syst Pharm* 2010; 67: 428–429.
- Connor TH, Sessink PJ, Harrison BR, et al. Surface contamination of chemotherapy drug vials and evaluation of new vial-cleaning techniques: results of three studies. *Am J Health Syst Pharm* 2005; 62: 475–484.
- Clark BA and Sessink PJ. Use of a closed system drug-transfer device eliminates surface contamination with antineoplastic agents. *J Oncol Pharm Pract* 2013; 19: 99–104.
- Sessink PJ, Trahan J and Coyne JW. Reduction in surface contamination with cyclophosphamide in 30 US hospital pharmacies following implementation of a

- closed-system drug transfer device. *Hosp Pharm* 2013; 48: 204–212.
21. Sessink PJ, Connor TH, Jorgenson JA, et al. Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device. *J Oncol Pharm Pract* 2011; 17: 39–48.
  22. Zock MD, Soefje S and Rickabaugh K. Evaluation of surface contamination with cyclophosphamide following simulated hazardous drug preparation activities using two closed-system products. *J Oncol Pharm Pract* 2011; 17: 49–54.
  23. Connor TH, Anderson RW, Sessink PJ, et al. Effectiveness of a closed-system device in containing surface contamination with cyclophosphamide and ifosfamide in an i.v. admixture area. *Am J Health Syst Pharm* 2002; 59: 68–72.
  24. Yoshida J, Tei G, Mochizuki C, et al. Use of a closed system device to reduce occupational contamination and exposure to antineoplastic drugs in the hospital work environment. *Ann Occup Hyg* 2009; 53: 153–160.
  25. Miyake T, Iwamoto T, Tanimura M, et al. Impact of closed-system drug transfer device on exposure of environment and healthcare provider to cyclophosphamide in Japanese hospital. *Springerplus* 2013; 2: 273.
  26. Wick C, Slawson MH, Jorgenson JA, et al. Using a closed-system protective device to reduce personnel exposure to antineoplastic agents. *Am J Health Syst Pharm* 2003; 60: 2314–2320.
  27. Yoshida J, Koda S, Nishida S, et al. Association between occupational exposure levels of antineoplastic drugs and work environment in five hospitals in Japan. *J Oncol Pharm Pract* 2011; 17: 29–38.
  28. Favier B, Labrosse H, Gilles-Afchain L, et al. The PhaSeal(R) system: impact of its use on workplace contamination and duration of chemotherapy preparation. *J Oncol Pharm Pract* 2012; 18: 37–45.
  29. US Pharmacopeia USP 800. Hazardous drugs—Handling in healthcare settings. 2014.
  30. Dorr RT and Alberts DS. Topical absorption and inactivation of cytotoxic anticancer agents in vitro. *Cancer* 1992; 70: 983–987.
  31. Ekhardt C, Gebretensae A, Rosing H, et al. Simultaneous quantification of cyclophosphamide and its active metabolite 4-hydroxycyclophosphamide in human plasma by high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (LC-MS/MS). *J Chromatogr B Analyt Technol Biomed Life Sci* 2007; 854: 345–349.
  32. Zhou J, Gao S, Zhang F, et al. Liquid chromatography-tandem mass spectrometry method for simultaneous determination of seven commonly used anticancer drugs in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci* 2012; 906: 1–8.
  33. Zhang W, Dutschman GE, Li X, et al. Quantitation of paclitaxel and its two major metabolites using a liquid chromatography-electrospray ionization tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2011; 879: 2018–2022.
  34. Licea-Perez H, Wang S and Bowen C. Development of a sensitive and selective LC-MS/MS method for the determination of alpha-fluoro-beta-alanine, 5-fluorouracil and capecitabine in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci* 2009; 877: 1040–1046.
  35. Garcia-Ac A, Segura PA, Viglino L, et al. Comparison of APPI, APCI and ESI for the LC-MS/MS analysis of bezafibrate, cyclophosphamide, enalapril, methotrexate and orlistat in municipal wastewater. *J Mass Spectrom* 2011; 46: 383–390.
  36. Karginova O, Siegel MB, Van Swearingen AE, et al. Efficacy of carboplatin alone and in combination with ABT888 in intracranial murine models of BRCA-mutated and BRCA-wild-type triple-negative breast cancer. *Mol Cancer Ther* 2015; 14: 920–930.
  37. Ganta S, Singh A, Kulkarni P, et al. EGFR targeted theranostic nanoemulsion for image-guided ovarian cancer therapy. *Pharm Res* 2015; 32: 2753–2763.