Surface contamination of chemotherapy drug vials and evaluation of new vial-cleaning techniques: Results of three studies

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Purpose. The results of three studies that describe the external contamination of chemotherapy drug vials are presented. New techniques for the improved decontamination of vials containing cisplatin are also described.

Summary. Study 1 evaluated the external contamination of drug vials with cyclophosphamide and ifosfamide in a pharmacy setting. Widespread contamination of the outside of drug vials was found with each drug. Study 2 evaluated the surface contamination of drug vials with cyclophosphamide and fluorouracil in three pharmacies. Sporadic contamination with fluorouracil was detected, while cyclophosphamide was found on most vials. In study 3, investigators compared the decontamination abilities of a standard decontamination procedure at the manufacturer level with an improved decontamination procedure and the use of sleeves to further decrease contamination. Though the methods of each study reported herein differed, the outcomes were similar. All chemotherapy drug vials studied demonstrated levels of contamination with the drug well above the limit of detection. Improved decontamination procedures, combined with the use of protective sleeves, reduced the level of platinum contamination by 90%, suggesting that standard decontamination procedures should be reconsidered.

Conclusion. The results of these studies are consistent with several others that have reported contamination of the outside surface of drug vials for a number of chemotherapy drugs. Contamination can be reduced by using decontamination equipment and protective sleeves during the manufacturing process.

Index terms: Antineoplastic agents; Cisplatin; Contamination; Cyclophosphamide; Decontamination; Fluorouracil; Ifosfamide; Injections; Manufacturing; Pharmacy; Vials

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The potential for pharmacy personnel and other health care workers to be exposed to chemotherapy and other hazardous drugs has increased over the past decade. Several factors have contributed to this increase, including the increase in the number of people with cancer,[1] the use of more combinations of chemotherapy drugs,[2] noncancer uses of chemotherapy drugs,[3] the development of more potent drugs,[4] specialized treatment procedures,[5] and increases in veterinary oncology.[6] These factors, along with the publication of several studies that revealed contamination of the workplace or exposure of health care workers to hazardous drugs, despite the use of proper engineering controls,[7-20] prompted the National Institute for Occupational Safety and Health (NIOSH) to

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publish an alert on antineoplastic and other hazardous drugs.[21] In 1999, a study conducted in the United States and Canada demonstrated widespread environmental contamination of both drug preparation and administration areas.[14] The results of a 2003 study showed both workplace contamination and worker exposure to two indicator drugs,[19] while another trial demonstrated workplace contamination with two drugs.[20] Some studies have shown reduction in workplace contamination or the presence of drugs in the urine after the adoption of containment devices.[22-26] However, background levels of several sentinel drugs continue to be measured, even when proper engineering controls and containment devices are in place.

Contamination of the workplace and subsequent worker exposure may result from several sources. The process of preparing the drug solution for delivery to the patient can result in the release of small amounts of the drug.[26] Larger spills of drugs happen less frequently but may contribute to long-term contamination of the workplace.[23] Treatment of the patient and disposal of residual drug solution in i.v. bags, i.v. tubing, and patient waste contribute to workplace contamination and the potential exposure of nursing personnel and housekeeping staff to these drugs.[12,17]

In addition to these sources of potential contamination, a number of European studies have demonstrated that the outer surfaces of the vials that contain these drugs are often contaminated with the drug (Table 1).[8,27-34] The sources of this contamination are not well understood but could be linked to the lack of cleaning or incomplete cleaning of the vials after filling, improper vial washing, contamination from broken vials after washing in storage or transport, or handling vials with contaminated hands or gloves.[35]

The three studies that follow describe the external contamination of chemotherapy drug vials. The drugs studied include the commonly used antineoplastic agents cyclophosphamide, ifosfamide, fluorouracil, and cisplatin. Although different analytical and sampling methods were used in each study, the techniques have been previously employed for the detection of low levels of these drugs. In the European study, widespread concern among pharmacy practitioners prompted one manufacturer to compare current decontamination procedures with two new methods of cleaning vials to determine the best way to reduce external contamination of vials.

Study 1: External contamination of drug vials with cyclophosphamide and ifosfamide in a pharmacy setting

Editor's note: The investigators for this study were Thomas H. Connor, Robert DeChristoforo, Jack R. Pretty, Raul M. Alfaro, and Lakisha M. Anderson. The views expressed are not necessarily the views of NIOSH, the National Institutes of Health (NIH), the Department of Health and Human Services (DHHS), or the U.S. government. Mention of a company or product name does not constitute endorsement by NIOSH, NIH, DHHS, or the U.S. government.

Methods. *Sampling procedures.* The wipe sampling of the chemotherapy vials was performed at the NIH Clinical Center Pharmacy Department in Bethesda, Maryland. Samples were collected from multiple lots of cyclophosphamide and ifosfamide received on different days over several months from routine orders received at the pharmacy. The pharmacy's prime vendor routinely places hazardous drugs, which are still in their original shipping cartons, in resealable plastic bags in sealed, labeled, rigid shipping containers separate from other pharmaceuticals. The vendor also uses air pillows to prevent breakage. Vials of cyclophosphamide contained 2 g of lyophilized powder for reconstitution and were all from one manufacturer (Mead Johnson Oncology Products, Princeton, NJ). Vials of ifosfamide contained 1 or 3 g of lyophilized powder for reconstitution and were obtained from two different manufacturers, American Pharmaceutical Partners (Schaumburg, IL) and Bristol-Myers Squibb (Princeton, NJ). The vials were transferred from the shipping containers to the biological safety cabinet and removed from their packaging, and the name, manufacturer, package size, lot number, expiration date, and physical nature of the vials were recorded. Sampling occurred in a biological-safety cabinet not used for the preparation of antineoplastic drugs to avoid possible cross-contamination and was conducted by an individual with experience in wipe sampling. Personal protective equipment was worn during sampling and gloves were changed after each vial was sampled. A surface wipe method described by Larson et al.[36] was used. A 55-mm filter paper disk[a] was wetted with 0.25 mL of solvent (10% acetonitrile,[b] 25% methanol,[b] and 65% Milli Q water) buffered at pH 6.0 and wiped over the entire vial surface. This procedure was repeated a second time. Both filter disks were placed in a 125-mL polypropylene jar,[c] and the jar was labeled with a code number and the date sampled. Six samples were taken from a single lot on each day, and the samples were stored at –80 °C until analysis. Once sampling was completed, the samples were shipped to NIOSH laboratories in Cincinnati, Ohio, on dry ice for analysis.

Sample preparation and analytical procedures. A total of 9.5 mL of the same solvent was added to the polypropylene jars to yield a total of 10 mL. After ultrasonication for 30 minutes, the solution was filtered into a 15-mL polypropylene tube through a 0.22 μM polyvinylidene fluoride syringe filter[d] to remove par-

Table 1.
Summary of European Studies of Vial Contamination[a]

Reference	Drug Assayed	Sampling Method	Results (*n* [%] Level of Contamination)
8	Fluorouracil	Wipe sample	0/20 (0%) positive (ampul)
	Cyclophosphamide		1/9 (11%) positive, 60 ng/vial
	Methotrexate		1/15 (7%) positive, 15,000 ng/vial
27	Cyclophosphamide	Wipe sample	105/140 (75%) positive, ND->2500 ng/5 vials
28	34 drugs	Visual inspection	154/6473 presumptive
			8/9 (89%) positive following analysis
29	Cisplatin	Wipe sample	49, 645, 28, 7, 19, 84 ng/vial[b] (6 batches)
30	Fluorouracil	Triple rinse of vial surface	3/90 (3%) positive
			4,800, 6,500, 18,100 ng/vial
31	Cisplatin	Wipe sample	2/6 (33%) positive
			37, 99 ng/vial
32	Fluorouracil	Water immersion with rotation for 30 sec	50 vials (100%), 403 ng/vial[b,c]
			100 vials (100%), 100 ng/vial[b]
			50 vials (100%), 2447 ng/vial[b]
	Cyclophosphamide		100 vials (100%), 11.9 ng/vial[b]
			50 vials (100%), 2.9 ng/vial[b]
	Ifosfamide		40 vials (100%), 13.1 ng/vial[b]
			100 vials (100%), 10.7 ng/vial[b]
	Etoposide		50 vials (100%), 583 ng/vial[b]
			100 vials (100%), 740 ng/vial[b]
	Docetaxel		33 vials (100%), 366 ng/vial[b]
	Doxorubicin		23 vials (100%), 29 ng/vial[b]
			47 vials (100%), 0.5 ng/vial[b]
33	Carboplatin	Wipe sample	30/30 (100%) positive, 7-251 ng/vial
	Cisplatin		4/30 (13%) positive, ND-9 ng/vial
	Cyclophosphamide		3/30 (10%) positive, ND-39 ng/vial
	Ifosfamide		1/30 (3%) positive, ND-344 ng/vial
	Methotrexate		12/30 (40%) positive, ND-18 ng/vial
34	Carboplatin	Solvent rinse	15, 50, 85 ng/vial[b] (3 batches)
	Ifosfamide		95, 44, 60, 95, 55 ng/vial[b] (5 batches)
	Fluorouracil		15, 65, 610, 61,000, 4.5, 1, 7 ng/vial[b] (7 batches)
	Cisplatin		6.24, 0.72, 2.91, 8.38, 0.16 ng/vial[b] (5 batches)

[a]ND = not detected.
[b]Mean value.
[c]Represents different manufacturers or different vial sizes.

ticulates. After filtration, 1.8 mL of filtrate was pipetted into a clean 15-mL tube and combined with 0.20 mL of ifosfamide or cyclophosphamide 1.0 µg/mL (whichever was not expected in the sample) to serve as 100 ng/mL of internal standard. The internal standard compensated for instrumental drift.

Analysis of cyclophosphamide and ifosfamide was adapted from Sottani et al.,[37] with some modifications. The reverse-phase high-performance liquid chromatography (HPLC) column used a stationary phase of C_{18}.[e] The mobile phase consisted of 55% methanol and 45% water, buffered to pH 6.0 using 0.010M ammonium acetate and acetic acid, with a flow rate of 0.23 mL/min. Elution times were approximately 4.2 and 4.9 minutes for ifosfamide and cyclophosphamide, respectively. The limit of detection (LOD) for ifosfamide and cyclophosphamide was 1.0 and 11 ng/vial, respectively.

Fifteen standards (plus a blank) covering the concentration range of 1–750 ng/mL (the approximate limit of the linear dynamic range) were included. Each standard and sample were injected three times, and the average response factor (analyte peak height divided by the internal standard peak height) was plotted for the standards. In addition, 12 cyclophosphamide and 10 ifosfamide control samples were run during the respective analyses. The mean recovery rate for cyclophosphamide was 103.1% (range, 90.8–110.7%) and 103.4% for ifosfamide (range, 98.8–108.8%).

Results. Two-gram vials of cyclophosphamide were sampled eight times on six different dates from a total of five lots from one manufacturer (Table 2). Six vials from a single carton were sampled for the presence of cyclophosphamide at the same time. All 48 samples had levels of contamination above 11 ng/vial (the LOD), ranging from 88 to 69,800 ng/vial, with a median concentration of 1,468 ng/vial.

One- and three-gram vials of ifosfamide were sampled on four different dates from a total of three lots from two manufacturers (Table 3). The single lot from one manufacturer had significantly higher levels of contamination (1478–1705 ng/vial, with detectable contamination on all six vials) than the two lots from the other manufacturer (3 [10%] of the 30 vials tested showed contamination above the LOD).

Table 2.
Cyclophosphamide Concentrations on the Outside of Drug Vials (n = 6)[a]

Lot	Expiration Date	Date Sampled	Mean (Range) Cyclophosphamide Conc. (ng/vial)
3A60735	6/04	3/7/03	2,654 (684–4,567)
3A60735	6/04	3/18/03	5,894 (2,129–8,837)
2M52756	6/04	3/18/03	1,456 (229–7,029)
2K64327	6/04	3/18/03	823 (743–956)
3A64230	7/04	3/28/03	357 (88–1,371)
3A64230	7/04	4/4/03	2,230 (143–8,182)
3C77989	9/04	4/21/03	34,124 (13,910–69,819)
3C77989	9/04	4/28/03	2,505 (1,464–3,545)

[a]All samples were taken from 2-g vials supplied by Mead Johnson.

Table 3.
Ifosfamide Concentrations on the Surface of Drug Vials[a]

Lot	Expiration Date	Vial Size (g)	Date Sampled	Range of Ifosfamide Conc. (ng/vial)
130138[b]	5/04	1	3/18/03	1660 (1478–1705)[c]
KFE08	6/05	3	4/7/03	<LOD[d]
KFE07	6/05	3	4/7/03	<LOD–12.9
KFE07	6/05	3	4/8/03	<LOD–13.4
KFE07	6/05	3	4/8/03	<LOD–12.2
KFE08	6/05	3	6/19/03	<LOD

[a]Each line of the table represents a box of six vials.
[b]Vials supplied by American Pharmaceutical Partners; all other vials supplied by Bristol-Myers Squibb.
[c]Presented as mean (range).
[d]LOD = limit of detection (11 ng/vial).

Conclusion. Surface contamination of commercially available drug vials was detected with both cyclophosphamide and ifosfamide.

Study 2: Surface contamination of drugs vials with cyclophosphamide and fluorouracil in a pharmacy setting

Editor's note: The investigators for this study were Bruce R. Harrison, Byron G. Peters, and Michael R. Bing. *This study was supported by an unrestricted educational grant from Carmel Pharma. The views expressed herein are not necessarily the views of the Department of Veterans Affairs or the U.S. government.*

Methods. *Drug vial sampling and processing.* This study of vial contamination was conducted in tandem with a study of surface contamination in three pharmacies.[20] Wipe samples were taken (usually on Friday) every other week after all preparations had been completed in the pharmacy. A single vial (multiple vials were sampled on three occasions at one institution) of cyclophosphamide or fluorouracil was selected at each site from the current pharmacy stock. All vials were in the original manufacturer's carton, and none of the samples were taken from cartons with evidence of broken vials or damaged cartons. Eighteen samples of each drug were taken at each of the three institutions.

Commercially available vials of fluorouracil 50-mg/mL (Pharmacia & Upjohn, (Kalamazoo, MI; American Pharmaceutical Partners) solution for injection (0.5-, 1-, 2.5-, and 5-g vials) and cyclophosphamide (Mead Johnson) lyophilized powder for reconstitution (0.5-, 1-, and 2-g vials) were tested.

Sample preparation and analytical procedures. All samples were collected using Cyto Wipe Kits.[f] Ten milliliters of 0.03M sodium hydroxide was applied over one of two sampling tissues provided.[8] The selected drug vials were then removed from the carton and sampled on a work surface that had been cleaned and decontaminated. All surfaces of one vial (cyclophosphamide or fluorouracil) were wiped thoroughly with one tissue by an individual experienced in sampling. This procedure was repeated with the second vial with the other tissue. Before and after the sampling of each pair of vials (cyclophosphamide and fluorouracil), the gloves were changed to avoid cross-contamination. Sample tissues were immediately placed in a single storage container, sealed, and stored at –20 °C or colder. After all samples were collected, they were shipped on dry ice to Exposure Control BV in the Netherlands for analysis.

Each sample was analyzed for the presence of cyclophosphamide by gas chromatography in tandem with mass spectroscopy–mass spectroscopy. Fluorouracil was analyzed by reverse-phase HPLC with ultraviolet-light detection. Methods for both analyses were developed by Sessink et al.[7,8,38] The analytical detection limit for cyclophosphamide and fluorouracil was 0.1 and 20 ng/mL of extract, respectively. This allowed detection of 16 ng of cyclophosphamide and 3200 ng of fluorouracil per respective vial after sample processing and dilution with reagents for analysis.

Results. Fuorouracil was found on 4 (7%) of the 54 samples. The quantities of fluorouracil found are shown in Table 4. Cyclophosphamide was found on 48 (89%) of the 54 samples. Three samples at one institution were obtained from six 1-g vials from a single carton rather than from a single vial, as was done with the other cyclophosphamide samples. All three of these samples were positive for cyclophosphamide. All 18 of the 2-g vials sampled at pharmacy C tested positive for cyclophosphamide, with concentrations ranging from 64 to 8782 ng/vial (median, 234 ng/vial). Three 2-g vials showed

Table 4.
Fluorouracil Concentrations Detected in Four Positive Samples[a]

Institution	Vial Size (g)	Manufacturer	Lot	Fluorouracil Conc. (ng/vial)
A	0.5	Pharmacia & Upjohn	FFA275	190560
B	1	American Pharmaceutical Partners	130043	630560
	0.5	Pharmacia & Upjohn	FFA274	8320[b]
C	5	American Pharmaceutical Partners	NR[c]	7680

[a]A total of 54 samples representing 61 vials were analyzed.
[b]This sample represents eight 0.5-g vials combined.
[c]Not recorded.

high levels of cyclophosphamide contamination (8782, 4256, and 1582 ng/vial). Cyclophosphamide concentrations detected on the 1-g vials ranged from less than 16 ng/vial (6 vials) to 480 ng/vial (median, 74 ng/vial). There was a significant difference in the median amount of cyclophosphamide detected in the two vial sizes (1 and 2 g) ($p = 0.0015$, median test). The quantity of cyclophosphamide found in each sample is shown in Table 5. Table 6 shows the amount of cyclophosphamide detected on vials with the same lot numbers sampled at different times, at different institutions, and from different cartons of drugs.

Conclusion. Surface contamination of commercially available fluorouracil and cyclophosphamide vials was demonstrated. Sporadic contamination with fluorouracil was detected, while cyclophosphamide was found on most vials.

Study 3: Surface contamination of drug vials with cisplatin reduced by improved cleaning techniques

Editor's note: The investigators for this study were Paul J. M. Sessink, Appie Bilos, and Gwendolyn Beckmann. Henk van Lier is acknowledged for his statistical support. The study was sponsored by Pharmachemie (a subsidiary of Teva Pharmaceutical Industries Ltd.), Haarlem, The Netherlands. Results from this study were presented in part at the Ninth International Symposium on Oncology Pharmacy Practice, Turin, Italy, 2004.

Methods. *Sample collection.* Monitoring of cisplatin vials (Pharmachemie, Haarlem) was chosen because of the large production volume of cisplatin, the high potential toxicity of the drug, and the availability of a very sensitive analytical method to determine cisplatin as platinum by stripping voltammetry.[39]

Five routine production lots of cisplatin were selected and decontaminated using differing methods. Surface contamination of vials from three lots (A, B, and C) with different sizes of vials and amounts of cisplatin, but with the same concentration of the drug, was measured and compared with the total absolute contamination (ng), contamination per surface area (ng/cm^2), and contamination related to the contents of the vial (ratio outside divided by the ratio inside). The results reflect the effect of the decontamination procedure as performed until early 2002 with standard decontamination equipment.

Next, improved decontamination equipment (vial washer) was introduced and evaluated using vials from lot D. The vial washer uses a more powerful and effective stream of water than the standard decontamination equipment and decontaminates the bottom of the vials.

After decontamination with the improved equipment, sleeves[g] were tightly shrunken around the vials (except the bottom of the vials) to encapsulate any cisplatin that was left on the outside of the vials and protect hospital workers from contact with the drug (lot E).

Of each of the five lots, 72–75 vials were randomly selected and tested. The characteristics of the lots are described in Table 7.

Extraction procedure. Each vial was placed in a separate container, and the containers were filled with 0.5M hydrochloride until the vials were completely immersed. The containers were then closed. After ultrasonification for 30 minutes, the vials were removed from the containers. During ultrasonification, vial surface contamination with cisplatin was assumed to be dissolved in the hydrochloride solvent. Throughout the entire sampling and extraction process, gloves were changed frequently to reduce any chance of cross-contamination, and the vials never came in contact with the gloved hand.

Sample pretreatment and analysis. Sample pretreatment and analysis with stripping voltammetry were performed using standard procedures.[39] Either 0.5 or 1.0 mL of the cisplatin extract was digested using hydrogen peroxide, hydrochloric acid, and ultraviolet light, resulting in the formation of platinum ions. Cisplatin contains approximately 65% platinum,[40] and analysis of platinum was performed in triplicate with a relative standard deviation of 2–3%. The LOD for cisplatin was 2 ng/L of extract. Samples were diluted and reanalyzed when high concentrations were discovered. Ten blank samples (empty vials) were extracted, analyzed, and compared with the cisplatin vials to correct for background values of platinum (50 ng/L of extract).

Statistical methods. Values of absolute amounts of contamination found on the vials of lots A, B, and C were compared using the Kruskal-Wallis test. The Wilcoxon rank sum test was used to compare lots B–D, C–E, and D and E. These tests were also used to compare the values of contamination per surface area, the values of contamination related to the contents of the vial, and all values corrected for blanks. A p value of ≤0.05 was considered significant. Data were char-

acterized by medians, ranges, and quartiles.

Results. *Evaluation of the decontamination procedure with the standard decontamination equipment.* Contamination of the vials with cisplatin is described in Table 8. Almost all vials in lots A, B, and C tested were contaminated with platinum. However, a large variation of contamination within the lots was observed. Significant differences ($p < 0.0001$) were observed among lots A, B, and C in absolute contamination and contamination with the contents of the vial ($p < 0.0001$). Absolute contamination increased, but the contamination related to the contents of the vial decreased with vial size. Contamination with the vial contents was higher than 10^{-6} for 30 vials of lot A, 15 vials of lot B, and 7 vials of lot C. No significant differences were observed in the contamination per surface area among lots A, B, and C.

Table 5.
Cyclophosphamide Concentrations Detected in All Samples in Study 2[a]

Institution/ Sampling Period	Vial Size (g)	Lot	Cyclophosphamide Conc. (ng/vial)
A/1	1	2J63724	480
A/2	1	2J63724	178
A/3	1	2J63726	224
A/4	1	2K64325	74
A/5	1	2J64325	ND[b]
A/6	1	2J64325	27
A/7	1	2L60109	26
A/8	1	2L60109	ND
A/9	1	2K60710	ND
A/10	1	3B62283	109
A/11	1	3B66172	ND
A/12	1	3B66172	72
A/13	0.5	3B63319	42
A/14	1	3B68537	248
A/15	1	3D66945	74
A/16	1	3D66945	32
A/17	1	3D73071	173
A/18	1	3D66945	107
B/1	1	2G45981	37
B/2	1	2J63724	307
B/3	1	2J63724	200
B/4	1	2K64328	ND
B/5	1	2E60915	82
B/6	1	2E60915	62
B/7	1	2K64328	22
B/8	1	2L60109	19
B/9	1	2L60109	ND
B/10	1	3A66953	128
B/11	1	3A66953	99
B/12	1	2L60109	30
B/13	1	3B66172	59
B/14	1	3B66172	66
B/15	1	2K60710	62
B/16	1	2K60710	934[c]
B/17	1	2J65817	270[c]
B/18	1	2J65817	570[c]
C/1	2	2G59973	85
C/2	2	2K60713	318
C/3	2	2J61803	194
C/4	2	2M48184	418
C/5	2	2M52756	64
C/6	2	2L60107	197
C/7	2	2L60107	238
C/8	2	3A71343	90
C/9	2	3A64230	69
C/10	2	3A71343	8782
C/11	2	3D69511	370
C/12	2	3D64725	4256
C/13	2	3D64725	1582
C/14	2	3D69511	182
C/15	2	3D71469	230
C/16	2	3D71469	138
C/17	2	3D71469	266
C/18	2	3F71589	443

[a] A total of 54 samples representing 69 vials were analyzed. All vials from Mead Johnson.
[b] ND = not detected (<16 ng/vial).
[c] Represents total concentration of six 1-g vials.

Effect of the improved decontamination equipment. To evaluate the effect of the improved decontamination machine, lots B and D were compared. All vials tested from lot D showed contamination with platinum; again, a large variation of contamination was observed. Significantly lower values of absolute contamination, contamination per surface area, and the contamination related to the contents of the vial were found after using the improved decontamination equipment compared with the standard decontamination equipment ($p < 0.0001$). Two vials cleaned with the improved decontamination equipment had values of contamination related to the vial contents higher than 10^{-6}.

It should be noted that 50% of the reduction in contamination can be explained by the lower cisplatin concentration of the vials in lot D (0.5 mg/mL) compared with lot B (1 mg/mL).

Effect of improved decontamination equipment in combination with sleeves. To evaluate the effect of the improved decontamination equipment in combination with the sleeves, lots C and E were compared. Most vials from lot E showed contamination with platinum, and a large variation of contamination was observed. However, lower values of absolute contamination, contamination per area surface, and contami-

Table 6.
Amount of Cyclophosphamide Detected on Selected 1-g Vials by Lot Number and Institution[a]

Lot	Cyclophosphamide Conc. (ng/vial)	Institution/ Sampling Period
2E60915	82	B/5
2E60915	62	B/6
2J63724	480	A/1
2J63724	178	A/2
2J63724	307	B/2
2J63724	200	B/3
2K64325	ND[b]	A/5
2K64325	27	A/6
2K64325	74	A/4
2K64328	ND	B/4
2K64328	22	B/7
2L60109	26	A/7
2L60109	ND	A/8
2L60109	19	B/8
2L60109	ND	B/9
2L60109	30	B/12
3A66953	128	B/10
3A66953	99	B/11
3B66172	ND	A/11
3B66172	72	A/12
3B66172	59	B/13
3B66172	66	B/14
3D66945	74	A/15
3D66945	32	A/16
3D66945	107	A/18

[a]Vials sampled on different sampling periods were drawn from different cartons of drugs. All vials from Mead Johnson.
[b]ND = not detected (<16 ng/vial).

Table 7.
Characteristics of the Lots Tested for Contamination with Platinum[a]

Characteristic	Lot A[b] (*n* = 73)	B (*n* = 73)	C (*n* = 72)	D (*n* = 75)	E (*n* = 75)
No. vials/lot	12,938	8,432	4,174	7,566	4,067
Vial size (mg)	10	50	100	25	50
Vial volume (mL)	10	50	100	50	100
Cisplatin conc. (mg/mL)	1	1	1	0.5	0.5
Surface area of vial (cm^2)	42	120	180	120	180
Decontamination equipment	Standard	Standard	Standard	Improved	Improved
Sleeve protection	No	No	No	No	Yes
Extraction volume (mL of HCl)	35	70	300	70	300

[a]All vials from Pharmachemie, Haarlem, The Netherlands.
[b]A, B, and C = standard decontamination procedure; D = improved decontamination procedure; E = improved decontamination procedure plus position-emission-tomography sleeves.

nation related to the contents of the vial were found for the improved decontamination equipment in combination with the sleeves compared with the standard decontamination equipment and the absence of sleeves ($p < 0.0001$). After being cleaned with the improved decontamination equipment in combination with the sleeves, one vial had a ratio of platinum concentration related to the vial contents of $>10^{-6}$.

Half of the reduction in contamination can be explained by the lower cisplatin concentration of the vials from lot E (0.5 mg/mL) compared with lot C (1 mg/mL); however, the overall reduction in contamination was about 90%, indicating that the improved decontamination equipment in combination with the sleeves was highly effective in reducing vial surface contamination.

To evaluate the effect of the sleeves themselves, lots D and E were compared. All parameters were significantly lower for the improved decontamination equipment in combination with the sleeves compared with the improved decontamination equipment without sleeves ($p < 0.0001$).

It should be noted, based on the comparison of the contamination of the vials from lot B to lot C, that an increase of absolute contamination and a small decrease of contamination related to the contents of the vial might be expected for the vials of lot E when compared with lot D. On the contrary, all contamination parameters were reduced, indicating a substantial effect when the sleeves were used.

Conclusion. The results of this study show the possibility to substantially reduce the surface contamination of drug vials with cisplatin and decrease the chance of hospital workers' exposure to the drug using improved decontamination equipment and sleeve protection of vials.

Discussion of results of all three studies

The results of these three studies clearly show that surface contamination exists on commercially available vials of cyclophosphamide, ifosfamide, fluorouracil, and cisplatin available in the United States and Europe. Sporadic contamination with fluorouracil was detected, cyclophosphamide and cisplatin were found on most vials, and ifosfamide was found on 25% of the vials tested. The detection of sporadic contamination with fluorouracil may be due to the fact that the assay is 200-fold less sensitive than that for cyclophosphamide.

The lot numbers of drug in the two U.S. studies (studies 1 and 2)

Table 8.
Platinum Contamination on the Surface of Cisplatin Drug Vials from Different Lots[a]

Value	Lot A ($n = 73$)			Lot B ($n = 73$)			Lot C ($n = 72$)			Lot D ($n = 75$)			Lot E ($n = 75$)		
	Absolute (ng)	Surface Area (ng/cm^2)	Ratio Out/In[b] ($\times 10^{-6}$)	Absolute (ng)	Surface Area (ng/cm^2)	Ratio Out/In ($\times 10^{-6}$)	Absolute (ng)	Surface Area (ng/cm^2)	Ratio Out/In ($\times 10^{-6}$)	Absolute (ng)	Surface Area (ng/cm^2)	Ratio Out/In ($\times 10^{-6}$)	Absolute (ng)	Surface Area (ng/cm^2)	Ratio Out/In ($\times 10^{-6}$)
Minimum	2	0.06	0.27	5	0.04	0.14	BV	BV	BV	3	0.02	0.17	BV	BV	BV
First quartile	4	0.12	0.64	13	0.11	0.41	18	0.11	0.29	6	0.05	0.36	2	0.01	0.06
Median	6	0.15	0.87	18	0.15	0.55	32	0.18	0.49	7	0.06	0.43	4	0.02	0.11
Third quartile	10	0.25	1.53	30	0.25	0.91	50	0.28	0.78	8	0.07	0.52	6	0.04	0.19
Maximum	150	3.59	23.07	256	2.13	7.87	112	0.63	1.73	79	0.66	4.85	146	0.81	4.49

[a]Values corrected for background values (BV). Lots A–C underwent standard decontamination. An improved decontamination procedure was used with lot D, and the improved decontamination procedure plus sleeve protection was used with lot E.
[b]Ratio out/in = contamination related to the contents of the vial.

were not sampled using a statistical approach. Vials were either selected from supplier shipments or drawn from the shelves. Nonetheless, several lot numbers of cyclophosphamide were represented by multiple vials and revealed some consistency in the amount of surface contamination detected, though the vials were sampled at different times and institutions and from different cartons of drugs. However, some exceptions to this were noted. In one pair of cyclophosphamide 2-g vials (lot number 3A71343), widely disparate values, 90 ng/vial versus 8782 ng/vial, were found. In another sample of six 2-g vials (lot number 2M52756), one vial had 7029 ng of cyclophosphamide on its surface, and the surface of the other five vials averaged only 387 ng/vial. In another lot (3C77989), six vials showed extremely high levels of drug (13,900–69,800 ng/vial) compared with the levels found on vials from most other lots of cyclophosphamide. Two fluorouracil vials showed very high levels of contamination, 190,000 and 630,000 ng/vial. These findings suggest possible contamination during vial filling or broken vials during transport from the manufacturer to the end user, although no evidence of the latter was observed in the samples selected.

In study 3, adequate samples were randomly selected from separate production batches, allowing statistical comparisons of the amount of contamination detected. Though nearly all vials were found to be contaminated with low levels of cisplatin, the range of values (<16–256 ng/vial) was far less than that found for cyclophosphamide and ifosfamide in the other two studies. Most importantly, the interventions introduced by the manufacturer significantly reduced the amounts of cisplatin detected in lots D and E. However, the sleeves used in this study did not cover the bottom of the vial at the time of sampling, which may have contributed to the residual contamination found in lot E. As a result, the manufacturer decided to invest in a completely automated sleeve applicator and shrinking equipment that will cover the bottom of the vials (TevaGuard, Teva Pharmaceuticals Ltd.). The reduction in external contamination is similar to reductions reported by Wachsmuth and Kittlaus[41] using a polypropylene container that encloses the vial.

Because the testing method using ultrasound to release any potential contamination from the outer surface of the vials results in much more vigorous agitation of the vials compared with normal handling in pharmacies, the actual exposure to hazardous residues will most likely be substantially lower than the values presented.

The wipe sampling methods used in studies 1 and 2 were similar to those reported by others.[8,19,27-34] However, efficiency of drug recovery from the surface of glass vials was not reported, nor was this tested. Kiffmeyer et al.[42] reported a 98% recovery of 5-fluorouracil from glass using a single simulated wipe test with 0.05M sodium hydroxide. Other methods of sampling for external contamination on glass vials include triple rinsing of the vial surface[30] and total immersion of the vial in the collection fluid,[32] similar to the method used in study 3. Delporte et al.[30] reported 92–100% recovery of fluorouracil from the surface of spiked vials using a triple-rinse technique. Recovery from the wipe sample methods used in studies 1 and 2 is likely less than 100%.[36,43] These methods can, at best, be used to estimate the least amount of external contamination expected.

The outer packaging associated with the cyclophosphamide, ifosfamide, and fluorouracil vials was not sampled in studies 1 and 2. The packaging material may also be a source of low-level drug contamination. Favier et al.[32] recovered over 1500 ng of fluorouracil from the outer packaging that had contained 25 5-g vials.

Given the propensity of cyclophosphamide to persist in a typical pharmacy environment[23] and the extremely high levels of drug found on some vials, it is not surprising that cyclophosphamide has been found any place the drug is handled, not just in the biological-safety cabinet. Favier et al.[32] made estimates of occupational exposure on the basis of results of their study of external contamination of vials containing fluorouracil, etoposide, docetaxel, and doxorubicin in addition to ifosfamide and cyclophosphamide. Fransman et al.[44] recently determined that the dermal pathway is a significant route of exposure for health care workers who handle cyclophosphamide.

Based on the results of studies 1–3 and the previously published reports,[8,27-34] external contamination of chemotherapy drug vials is one of several sources of drug residues detected on pharmacy surfaces and in the urine of pharmacy personnel. As suggested by several authors,[19,30,32,33,42] current practices should be changed to include safe-handling precautions when opening chemotherapy drug packaging before drug preparation in the pharmacy.

Personnel working in warehouses and storage areas should also be made aware of the potential contamination of the vials and be instructed to use personal protective equipment when appropriate. Outer packaging that has come into contact with hazardous drug containers should be disposed of as trace-contaminated hazardous waste in the same waste stream as chemotherapy gowns, gloves, and wipes used to prepare antineoplastic drugs. Attention to this problem at the manufacturer level, the introduction of improved decontamination equipment, and the use of sleeve protectors could significantly decrease the amount of chemotherapy drug contamination found in pharmacies at user levels.

All manufacturers of hazardous drugs should strive to provide drug vials whose external surfaces are as free of drug contamination as possible. While it may not be practical to attain and document the complete absence of contamination, users must be warned of the possibility of contamination and take appropriate steps to prevent exposure. This information should be contained in the Material Safety Data Sheets and in the package labeling.

Conclusion

The results of these studies are consistent with several others that have reported contamination of the outside surface of drug vials for chemotherapy drugs. Contamination can be reduced by using decontamination equipment and protective sleeves during the manufacturing process.

Since this manuscript was submitted for publication, MedWatch reports were submitted to the Food and Drug Administration for each of the drugs involved in study 1. The reports were subsequently forwarded to the respective manufacturers. It should be noted that Mead Johnson Oncology Products, listed as the manufacturer of Cytoxan (cyclophosphamide), is a Bristol-Myers Squibb (Princeton, NJ) company and that Baxter Healthcare Corporation (Deerfield, IL) manufactures Ifex (ifosfamide) for Bristol-Myers Squibb. After this survey was conducted, Bristol-Myers Squibb announced that Cytoxan will no longer be a lyophilized product and will be manufactured by Baxter Healthcare Corporation. Cytoxan will continue to be distributed by Bristol-Myers Squibb Oncology.

After receiving the MedWatch reports, the authors were contacted by an Associate Director Corporate Quality, Health, and Safety for Bristol-Myers Squibb, first by written correspondence and then by telephone. He explained that the standard practice of Bristol-Myers Squibb is to use an external vial washer to clean all oncology product vials before labeling. This operation is followed by a 100% visual inspection for visual defects, including the presence of surface residues. Although there are currently no official specifications (current good manufacturing practices), industry standards, or guidelines that reference limits for residues of drugs on exterior surfaces of vials, Bristol-Myers Squibb has started conducting some experimental work to assess potential surface residues on the exterior of vials for potent compounds. Its written response indicated that it would investigate optimized surface cleaning methodology through technological improvements. After follow-up correspondence and further review of the data, it stated that it is expediting changes to the information provided on both their Material Safety Data Sheets and package inserts for its chemotherapy drug products. The new wording will emphasize the importance of always wearing protective gloves when handling product containers.

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[a]No. 42 ashless 55-mm filter paper disk, Whatman, Middlesex, United Kingdom.

[b]Optima grade, Fisher Scientific, Pittsburgh, PA.

[c]125-mL, wide-mouth, screw cap, polypropylene jar, Fisher Scientific.

[d]Syringe filters, Fisher Scientific.

[e]Luna C_{18} column, 15 cm × 2.0 mm i.d., 5-µM silica particle size, 100-Å pore size, Phenomenex Inc., Torrance, CA.

[f]CytoWipe Kits, Exposure Control B.V., Wijchen, The Netherlands.

[g]Monoaxial, stretched, high-shrink polyethylene terephtalate film.

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