Irene Krämer*, Matteo Federici and Rudolf Schierl

Environmental and Product Contamination during the Preparation of Antineoplastic Drugs with Robotic Systems

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Abstract

Background: Robotic systems are designed to minimize the exposure to antineoplastic drugs during automated preparation. However, contamination cannot be completely excluded. The aim of the study was to evaluate the contamination with antineoplastic drugs on the working surfaces and on the outer surface of the ready-to-use products (infusion bags and syringes) during automated preparation with different versions of a robot and manual preparation.

Methods: Surface contamination with platinum (Pt) and 5-fluorouracil (5-FU) was measured by wipe sampling and quantified by voltammetry for Pt and GC-MS for 5-FU. Sampling was performed on pre-defined locations in the working areas before and after preparation of standardized test products. The outer surfaces of Pt- or 5-FU-containing infusion bags and 5-FU-containing syringes were sampled without and after manual capping.

Results: Overall, the surface contamination in the working areas of the robotic system ranged from 0.4 to 114 pg/cm^2 for Pt and from 1.3 to 1,250,000 pg/cm^2 for 5-FU. The highest contamination levels were detected after preparation on the gripper of the robotic arm and on the surface beneath the dosing device. In most cases, measured concentrations were higher after preparation. Outer surfaces of infusion bags prepared with the robotic system were less contaminated than manually prepared bags. Contamination on the outer surface of syringes varied depending on the procedure adopted.

Conclusions: The risk of contamination is localised inside the working area of the robot. The outer surfaces of products were only marginally contaminated. Cleaning procedures of the working area are to be further investigated. An effective decontamination procedure for the working area of the robot and automated capping of filled syringes should be developed to further minimize the occupational risk.

Keywords: antineoplastic drugs, surface contamination, wipe sampling, automated compounding, voltammetry, gas chromatography/mass spectrometry

***Corresponding author: Irene Krämer,** Department of Pharmacy, University Medical Center, Johannes Gutenberg-University Mainz, Langenbeckstraße 1, 55131, Mainz, Germany, E-mail: irene.kraemer@unimedizin-mainz.de
Matteo Federici, Department of Pharmacy, University Medical Center, Johannes Gutenberg-University Mainz, Langenbeckstraße 1, 55131, Mainz, Germany, E-mail: mtt.federici@gmail.com
Rudolf Schierl, Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany, E-mail: Rudolf.Schierl@med.uni-muenchen.de

Introduction

Since many antineoplastic drugs used for anti-cancer therapy are classified as hazardous on the basis of carcinogenicity and reproductive toxicity, healthcare practitioners have to be protected from occupational exposure during preparation and administration of these medicinal products [1, 2]. Exposure to antineoplastic drugs in the workplace has been associated with acute and short-term as well as long-term effects [3]. Absorption via the skin represents the most likely absorption route and may be caused by touching contaminated surfaces [4]. Recent environmental exposure studies highlighted that the preparation areas are still frequently contaminated with antineoplastics despite of the implementation of safety policies and advanced technical equipment over the last decades [5, 6]. Because it is impossible to reduce the external exposure during handling of antineoplastic drugs to zero, it should be kept “as low as reasonably achievable” (ALARA principle). Surface wipe sampling is considered the method of choice to assess the risk of occupational exposure and to determine the effectiveness of safe handling procedures in healthcare settings [7, 8].

Biological safety cabinets and protective devices are widely recognized to minimize the external exposure during the handling of antineoplastic drugs. More recently semi-automatic and automatic compounding devices were established. They are designed to improve patient

safety by consistent and accurate automated procedures and complete traceability of the drug preparation process as well as worker safety by limiting exposure to leakages and aerosols of the hazardous drugs. Moreover, the risk of needle stick injuries and physical complaints by repetitive motion are diminished. However, contamination of the outer surfaces of the ready-to-administer preparations cannot be totally excluded. Thereby the hazardous residues may be transferred to the preparation and even administration areas. Until now, only few studies have been published regarding workplace contamination during automated compounding [9–12].

The aim of this study was to measure the levels of contamination with antineoplastic drugs (5-fluorouracil and platinum-based anticancer drugs) by surface wipe sampling in the working area and on finished products (infusion bags, syringes) during automated compounding with robotic systems.

Methods

Study site

The study was conducted in the centralized cytotoxic drug preparation unit of the Pharmacy Department of the University Medical Center Mainz (Germany). Antineoplastic products like infusion bags and ready-to-administer (RTA) syringes are prepared in two Class II biological safety cabinets (BSC) and a fully automated robotic system (currently: APOTECAchemo Rev. C, Loccioni Group, Italy) in the same Grade C cleanroom. The annual workload amounted in 2017 to 50.000 preparations from which one third were prepared automatically.

Studies were performed with different types and versions of the fully automated robotic system (compare Figure 1). The primarily installed robotic system CytoCare (Health Robotics, Italy) was upgraded in 2011 (hardware and software) to the APOTECAchemo Rev. B (Loccioni Group, Italy) and operated over several years. In late 2016 the robot was replaced by APOTECAchemo Rev. C. Currently, the robot is programmed to process 31 different antineoplastic drugs and different types and sizes of primary packages (i. e. single-use syringes and prefilled infusion bags). The average output amounts to 12 preparations/hour and maximum 90 preparations/working day.

Robotic system

The robotic system (Figure 2) comprises a working area with a negative pressure gradient and vertical laminar airflow, where a six-axis anthropomorphic robotic arm is installed. The area refers to a Grade A cleanroom environment. In the loading area, a sliding door allows the access to the rotating carousel where starting materials and finished products are temporarily stored. The operator's involvement is limited to load the starting materials and to remove the finished products placed on a rotating carousel for unloading. The working area is only accessed by the operator for decontamination and cleaning. Barcode recognition, photographic recognition of the source products, and gravimetric verification of the measured volumes are used for in-process controls and process documentation. Further details can be found in the literature [13–18].

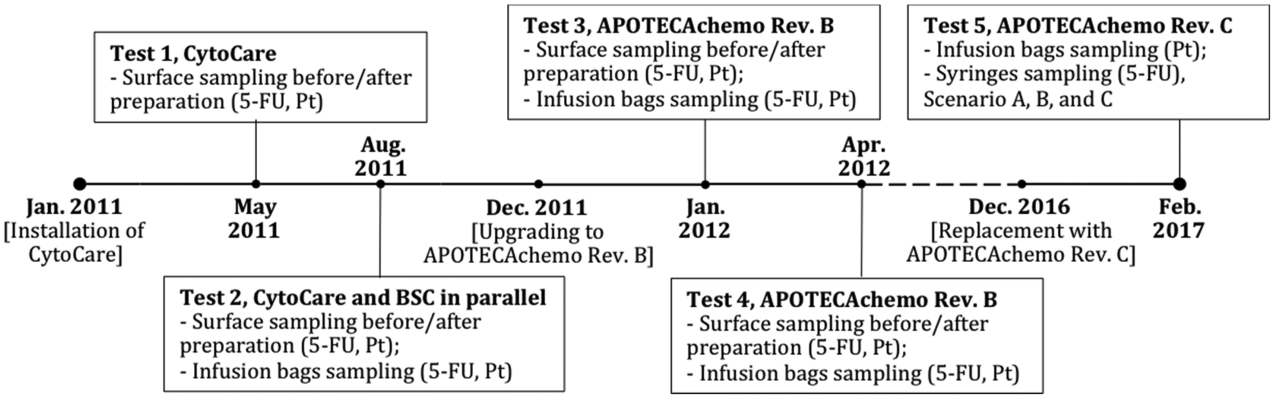

Figure 1: Timeline of changes of the robotic system and wipe tests conducted at different time points.

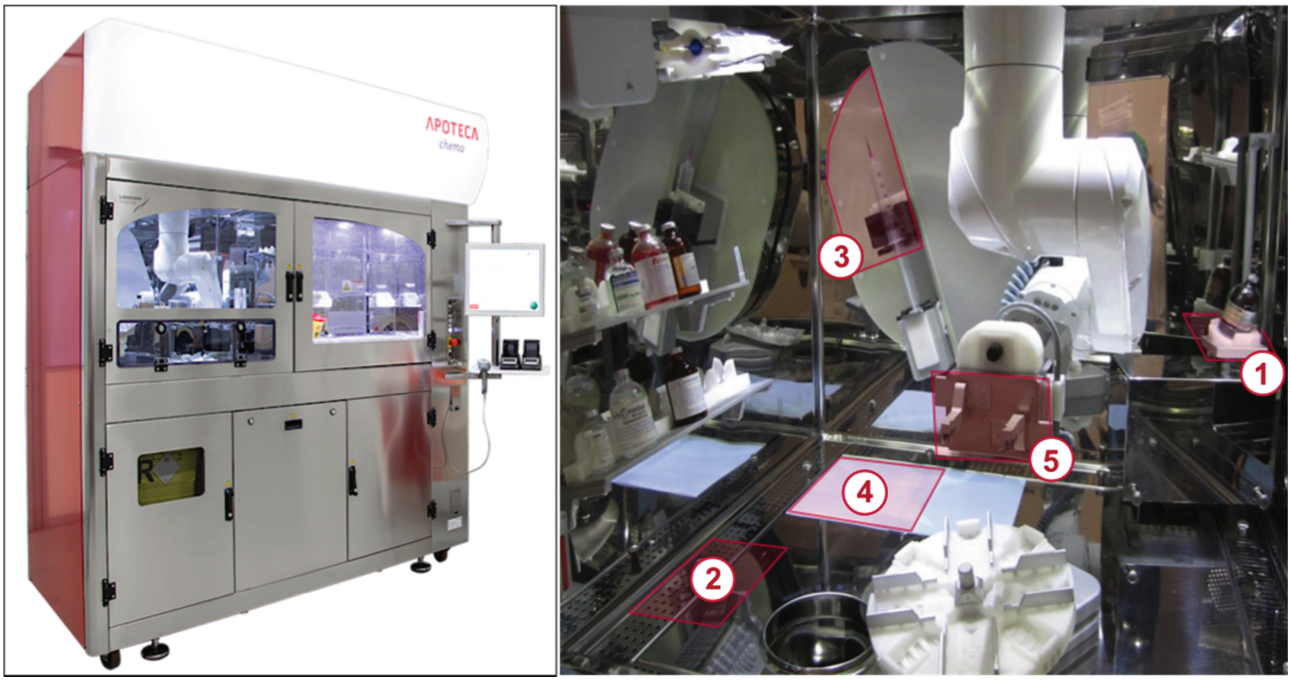

Figure 2: Robotic system APOTECAchemo, Loccioni Group, Italy, (left side in total); working area (right side) with marked sampling sites: (1) balance, (2) surface beneath the shelves, (3) dosing device, (4) surface beneath the dosing device, (5) gripper of the robotic arm.

Manual preparation in the BSC

Manual aseptic preparation is performed in the biological safety cabinet (compare Figure 3) (BernerFlowSafe® C-[MaxPro]^3–130, BERNER International GmbH, Elmshorn, Germany) by experienced pharmacy technicians either volume or weight based using BD-Cato® Medication Workflow Solutions (Becton Dickinson GmbH, Vienna, Austria). The preparation process is performed on a single-use, liquid-proof, absorbent preparation pad (Blue lab prep mats, BERNER International GmbH, Elmshorn, Germany), which is changed every 30 min.

Personal protective equipment (PPE)

Protective clothing is used according to the guidelines for aseptic handling of antineoplastics.

Double gloving consists of non-sterile nitrile gloves, covered by sterile latex gloves during manual preparation and operating at the loading area of the robot. The change time of the outer gloves is 15 min during manual preparation and 30 min during automated preparation.

Cleaning procedures of the robotic system and BSC

Daily cleaning procedure of APOTECAchemo: at the end of a working shift critical surfaces in the working area (i. e. gripper of the robotic arm, dosing device, balance) and loading area (i. e. entrance surface, sliding door) are decontaminated by wiping with sterile compresses soaked with 0.05 molar ethanolic sodium hydroxide solution to remove potential cytotoxic contamination. Afterwards, the surfaces are disinfected by wiping with spore-free alcohol (Perform advanced Alcohol EP, Schülke, Germany) to remove viable microorganisms. Finally, UV irradiation of the surfaces inside the working area is performed over a period of 4 h.

Weekly cleaning procedure of APOTECAchemo: at the end of the working shift at Wednesdays all surfaces in the working and loading area are decontaminated by wiping with sterile compresses soaked with 0.05 molar ethanolic sodium hydroxide solution and afterwards disinfected by wiping with spore-free alcohol (Perform advanced Alcohol EP, Schülke, Germany) and UV irradiated for 4 h.

Daily cleaning procedure of the BSC: Surfaces of the BSC (i. e. back and side walls, front window, working surface) are disinfected by wiping with spore-free alcohol (Perform advanced Alcohol EP, Schülke, Germany). The working surface is disinfected every 30 min.

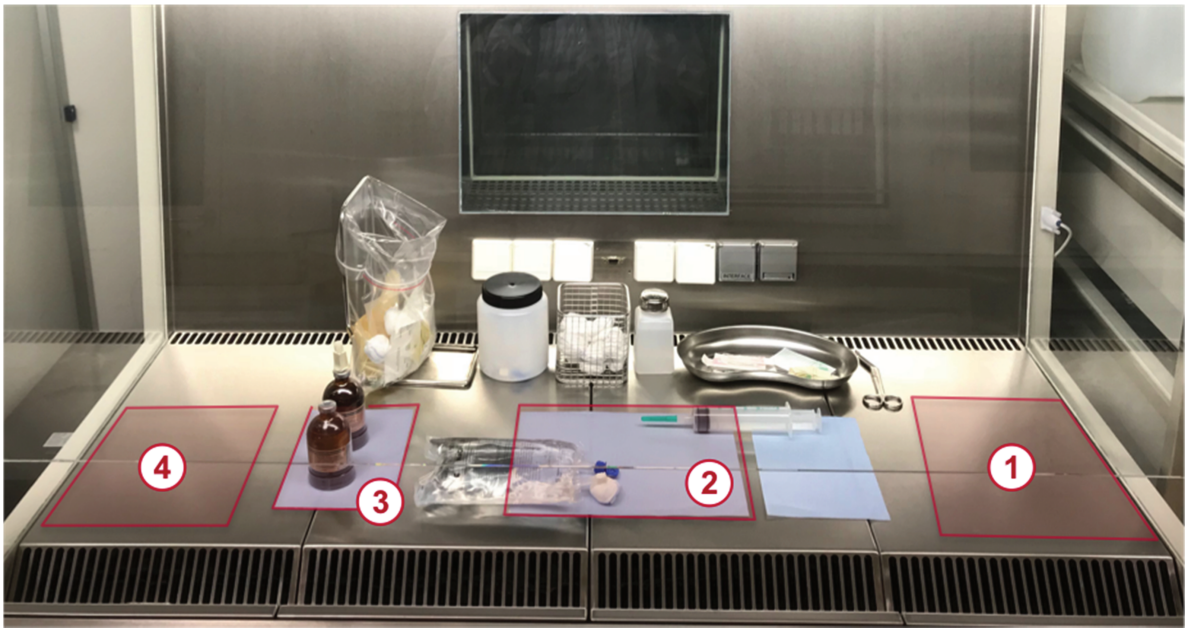

Figure 3: Sampling sites inside the biological safety cabinet (BSC): (1) surface right side, (2) mat for preparation, (3) mat for vial storage, (4), surface left side.

Biweekly cleaning procedure of the BSC: Surfaces of the BSC are decontaminated by wiping with 0.05 molar ethanolic sodium hydroxide solution and disinfected by wiping with a sporicidal disinfection solution (Perform sterile PAA, Schülke, Germany).

Surface wipe sampling

Standardized products containing either 5-fluorouracil (5-FU) or platinum-based anticancer drugs (Pt) were aseptically prepared in series according to the standard operating procedures. Prior to the preparation sessions, the working areas were cleaned in accordance to the facility's standard procedure as given above. Wipe sampling in the working areas of the robotic system and of the BSC was performed before preparation (BP) (i. e. after cleaning) and after preparation (AP) on pre-defined sampling points and on the outer surfaces of preparations.

Surface wipe sampling in the working area of the robotic system

Wipe sampling inside the robotic system was performed at four different time points (Test 1–4, Figure 1). 15 infusion bags containing 1200 mg 5-FU each and 15 infusion bags containing Pt-based antineoplastic drugs, i. e. 5 bags containing 40 mg cisplatin or 120 mg oxaliplatin or 450 mg carboplatin, were automatically prepared in series on two consecutive days. Prefilled infusion bags (500 mL 0.9 % NaCl or 5 % glucose solution, Freeflex, Fresenius Kabi, Germany) were used as vehicle solutions and primary packages. The following surface areas (see Figure 2) were sampled BP and AP:

1. Surface of the balance (45 cm^2), where the vials containing the antineoplastic product and the infusion bags are placed and weighed during the preparation process
2. Surface area beneath the shelves (270 cm^2), on which the antineoplastic drug vials are temporarily stored during the preparation process
3. Dosing device (400 cm^2), where the syringe is fixed during the withdrawal of antineoplastic drug solutions from the vials and the injection into the infusion bags
4. Surface area beneath the dosing device (400 cm^2)
5. Gripper of the robotic arm (180 cm^2), which grasps the needed items during the preparation process, such as vials, syringes, and infusion bags.

Surface wipe sampling in the BSC working area

Surface wipe sampling during manual preparation was performed once (Test 2, Figure 1). 15 infusion bags containing

1200 mg 5-FU each and 15 infusion bags containing Pt-based anticancer drugs were manually prepared on two consecutive days by an experienced pharmacy technician in the BSC. The required amounts of concentrated drug solutions were withdrawn from the vials into a syringe (Original Perfusor®-Spritze, B. Braun Melsungen AG, Germany) via a CODAN-Spike (CODAN GmbH, Lensahn, Germany) and injected into the infusion bag via a needle (Sterican® Standardkanülen, B. Braun Melsungen AG, Germany). Four surface areas inside the BSC were sampled BP and AP (Figure 3):

1. Surface area at the right side of the BSC (400 cm^2), where disposables and drug vials needed for the preparation are inserted
2. Single-use, waterproof mat (400 cm^2), on which the manual compounding is performed
3. Single-use, waterproof mat (266 cm^2), where the drug vials are temporarily stored during the preparation process
4. Surface area at the left side of the BSC (400 cm^2), where the finished products are placed.

Wipe samples were also taken from the surface of the outer latex gloves worn by the pharmacy technician. Sampling was performed before starting the preparation and at the end of a 15 min glove wearing period.

Surface wipe sampling of Pt-, 5-FU-containing infusion bags

Contamination levels of Pt or 5-FU were determined on the outer surface of the infusion bags (400 cm^2) prepared with the CytoCare (15 preparations each, Test 2), the APOTECAchemo Rev. B (15 preparations each Test 3, 4), and manually in the BSC (15 preparations each Test 2). 15 infusion bags containing 70 mg cisplatin were prepared with APOTECAchemo Rev. C and wipe sampled (Test 5).

Surface wipe sampling of 5-FU containing syringes

Test products were automatically prepared in the APOTECAchemo Rev. C (Test 5). Pre-assembled APOTECAchemo-syringes with a nominal volume of 20 mL (ASN-20, Drug compounding dosing device, Loccioni Group, Italy) were used as primary packaging material. The ASN-20 are 3-piece single-use syringes with a four ribs plunger structure, and a Luer-lock tip connected to a vented needle, which ensures pressure equalization during the withdrawal of drug solution from the vial. The syringes were filled in series by withdrawal of 15 mL 5-FU injection solution from a 100 mL vial (5-FU 50 mg/mL, Medac, Germany). Wipe sampling was performed by wiping thoroughly the outer surface of each RTA-syringe including the exposed plunger, the barrel, and the Luer-lock tip/cap (the sampled area was calculated approximately 110 cm^2). The syringes were sampled at the end of the automated preparation process either with or without manual capping (mC). Capping of the automatically filled syringes is manually performed by the operator after unloading the filled syringes. Unloaded syringes are still connected to the vented filling needle. The mC procedure consists of (1) de-connecting of the vented needle, (2) removing the air from the syringe tip, and (3) capping the syringe with a tip cap (Combi-Stopper, B. Braun Melsungen AG, Germany). Wipe sampling on the outer surface of the filled syringes was carried out considering three different scenarios. In scenario A, wipe sampling was performed without manual processing (syringe 1–10). In scenario B, wipe sampling was performed after mC by an inexperienced operator (syringe 1–15), while in scenario C the mC procedure was performed by an experienced operator (syringe 1–10).

Quantitative analysis of the wipe samples

Wipe samples were taken by using a validated surface monitoring kit developed and provided by the Institute for Occupational, Social, and Environmental Medicine of the University of Munich (Germany). Sampling was carried out according to a validated method previously published by Schmaus et al. [19]. Each sample site was wiped in three different directions using filters previously moistened with an appropriate solvent (0.1% hydrochloric acid for Pt, methanol for 5-FU). Typically, a delineated surface area measuring 400 cm^2 was sampled. For some specific items on which the areas were smaller, the actual size sampled was calculated. After wiping, the filters were transferred to a screw-cap glass container, stored at 4 °C (Pt samples) or at −20 °C (5-FU samples), and sent overnight to the laboratory for analysis to the Institute for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich. The wipe samples were analysed as described in detail for Pt [19] and 5-FU [20]. Briefly, after adding 0.5 N hydrochloric acid, the samples intended for Pt analysis were processed using ultraviolet radiation and

the total amount of Pt was determined by inverse voltammetry. 5-FU concentrations were quantified by gas chromatography/mass spectrometry (GC-MS) using methanol as organic solvent for drug extraction and 5-chlorouracil as internal standard (IS). Concentrations were determined via the ratio of the peak areas of 5-FU and IS using a previously generated standard curve that is linear from 1 to 50 ng. Samples with higher concentrations than used to prepare the calibration curve, were diluted accordingly. From each container a sample was withdrawn and injected once. The limits of detection (LODs) were 0.02 ng/sample, i. e. 0.05 – 0.4 pg/cm^2 for Pt and 0.2 ng/sample, i. e. 0.5 – 4.4 pg/cm^2 for 5-FU. The concentrations of Pt and 5-FU were calculated in ng/sample and reported in pg/cm^2 surface area wiped.

Results

The concentrations of 5-FU and Pt in wipe samples taken from the predetermined surfaces inside the CytoCare, the APOTECAchemo Rev. B, and the BSC before and after preparation of 5-FU or Pt containing test products are listed in Tables 1 and 2, see also [21, 22]. The concentrations of 5-FU and Pt in wipe samples taken from the outer surfaces of the finished products are listed in Tables 3 and 4.

CytoCare (Test 1, 2)

In total 40 wipe samples were taken inside the robotic system CytoCare. Concentrations of Pt and 5-FU exceeded the LODs in 100 % and 90 % of the wipe samples (n = 20). The levels of contamination ranged from 0.4 pg/cm^2 to 114.4 pg/cm^2 for Pt and from 1.3 to 1,250,000 pg/cm^2 for 5-FU. In general, the levels of contamination were lower before preparation, i. e. after decontamination with ethanolic sodium hydroxide solution than after preparation of the test products. The highest contamination levels were found after the preparation procedure on the surface beneath the dosing device (5-FU) and on the gripper of the robotic arm (Pt) after preparation of the test products.

Table 1: Contamination with 5-fluorouracil (5-FU) during robotic preparation of 5-FU infusion bags with CytoCare, APOTECAchemo Rev. B, and manual preparation in a biological safety cabinet (BSC).

	CytoCare				APOTECAchemo Rev. B				BSC		
	Test 1 (May 2011)		Test 2 (Aug. 2011)		Test 3 (Jan. 2012)		Test 4 (Apr. 2012)		Test 2 (Aug. 2011)		
Sampling area (size)	5-FU (pg/cm^2)				5-FU (pg/cm^2)				Sampling area (size)	5-FU (pg/cm^2)	
	BP*	AP**	BP	AP	BP	AP	BP	AP		BP	AP
(1) Balance (45 cm^2)	5.3	172.2	nd	5.0	13.2	nd	nd	nd	(1) BSC surface right side (400 cm^2)	1.8	nd
(2) Surface area beneath the shelves (270 cm^2)	2.2	145.6	19.6	3.0	nd	nd	3.0	0.7	(2) Mat for preparation (400 cm^2)	0.8	1,725,000
(3) Dosing device (400 cm^2)	12.0	1.3	7.8	nd	nd	4.0	2.8	625.0	(3) Mat for vial storage (266 cm^2)	nd	67.4
(4) Surface area beneath the dosing device (400 cm^2)	33.0	1,250,000	2.3	2.3	3.5	1.3	nd	nd	(4) BSC surface left side (400 cm^2)	nd	3.0
(5) Gripper of the robotic arm (180 cm^2)	1,791.7	3,124.0	601.7	428.9	8.3	352.2	58.3	4,933.3	(5) Gloves (400 cm^2)	nd	726.5

*BP: before preparation (after daily cleaning procedure), **AP: after preparation; nd: below detection limit of 0.2 ng 5-FU/sample.

Table 2: Contamination with platinum (Pt) during robotic preparation of Pt infusion bags with CytoCare, APOTECAchemo Rev. B, and manual preparation in a biological safety cabinet (BSC).

	CytoCare				APOTECAchemo Rev. B				BSC		
	Test 1 (May 2011)		Test 2 (Aug. 2011)		Test 3 (Jan. 2012)		Test 4 (Apr. 2012)		Test 2 (Aug. 2011)		
Sampling area (size)	Pt (pg/cm^2)				Pt (pg/cm^2)				Sampling area (size)	Pt (pg/cm^2)	
	BP *	AP * *	BP	AP	BP	AP	BP	AP		BP	AP
(1) Balance (45 cm^2)	0.4	5.9	1.4	3.7	1.3	0.4	2.6	0.9	(1) BSC surface right side (400 cm^2)	1.3	1.4
(2) Surface area beneath the shelves (270 cm^2)	5.4	7.2	4.9	14.8	1.5	0.9	2.7	1.9	(2) Mat for preparation (400 cm^2)	0.1	0.2
(3) Dosing device (400 cm^2)	0.9	1.6	10.4	58.0	43.0	3.5	14.4	6.2	(3) Mat for vial storage (266 cm^2)	0.1	16.7
(4) Surface area beneath the dosing device (400 cm^2)	8.7	13.6	20.6	35.5	1.7	1.7	1.4	1.1	(4) BSC surface left side (400 cm^2)	0.6	0.3
(5) Gripper of the robotic arm (400 cm^2)	3.0	9.1	6.4	114.4	3.9	3.5	3.2	1.8	(5) Gloves (180 cm^2)	0.1	34.5

*BP: before preparation (after daily cleaning procedure), **AP: after preparation; LOD = 0.02 ng Pt/sample.

APOTECAchemo Rev. B (Test 3, 4)

In total 40 wipe samples were taken inside the robot APOTECAchemo Rev. B. Concentrations of Pt and 5-FU were in 100 % and 60 % of the wiped surfaces above the limit of detection, respectively. The surface contamination ranged from 0.4 to 43.0 pg/cm^2 for Pt and from 1.3 to 4,933.3 pg/cm^2 for 5-FU. The highest concentrations of 5-FU were detected on the gripper of the robotic arm after the preparation procedure (352.2 pg/cm^2 (Test 3), 4,933.3 pg/cm^2 (Test 4). Considerable residues of Pt and 5-FU were also observed on the dosing device with a maximum of 43.0 pg/cm^2 for Pt and 625.0 pg/cm^2 for 5-FU. In most cases, concentrations of Pt and 5-FU reached the same order of magnitude before and after preparation.

BSC (Test 2)

The 20 wipe samples taken during manual preparation of the test products revealed Pt and 5-FU concentrations above the LOD in 100 % and 60 % of the samples, respectively. Contamination was mainly observed on the mat where the preparation procedure was performed, the mat where the drug vials were temporarily stored, and on the gloves worn by the pharmacy technician during the procedure. The highest levels of contamination were detected after preparation amounting to 1,725,000 pg/cm^2 of 5-FU on the mat for preparation and 34.5 pg/cm^2 of Pt on the surface of the gloves. Samples taken before preparation contained only traces of cytotoxic drugs.

Infusion bags

A total of 135 infusion bags were sampled, of which 105 products were automatically prepared and 30 products were manually prepared (see Table 3). The drug concentrations on automatically prepared infusion bags ranged from < 0.05 to 24.5 pg/cm^2 (median 0.1 ± 3.8 pg/cm^2) for Pt and from < 0.05 to 791.5 pg/cm^2 (median 2.8 ± 188.2 pg/cm^2) for 5-FU. Thereby low contamination levels of Pt were detected on the automatically prepared infusion bags, independent from the version of the robotic system used. Elevated concentrations of 5-FU were measured on infusion bags prepared with the CytoCare (150.8, 242.5, 560.5 pg/cm^2) and in a single case with the APOTECAchemo Rev. B (791.5 pg/cm^2). Drug concentrations on manually prepared infusion bags ranged from < 0.05 to 47.8 pg/cm^2 for Pt and from not detectable to 19.5 pg/cm^2 for 5-FU. In no case upper outliers of 5-FU concentrations were observed during manual preparation.

Table 3: Levels of contamination with platinum (Pt) or 5-fluorouracil (5-FU) during preparation infusion bags with the robotic systems CytoCare, APOTECAchemo Rev. B, APOTECAchemo Rev. C and manual preparation in a biological safety cabinet (BSC). Samples (400 cm^2) were taken from the outer surfaces of the infusion bags.

Type of sample area (400 cm^2 per bag)	CytoCare	APOTECAchemo Rev. B		APOTECAchemo Rev. C	BSC
	Test 2 (May 2011)	Test 3 (Jan. 2012)	Test 4 (Apr. 2012)	Test 5 (Feb. 2017)	Test 2 (Aug. 2011)
	Pt (pg/cm^2)		Pt (pg/cm^2)	Pt (pg/cm^2)	Pt (pg/cm^2)
Infusion bag Pt 01	1.3	0.2	0.1	0.3	0.6
Infusion bag Pt 02	0.2	nd	0.4	0.3	0.8
Infusion bag Pt 03	3.2	0.3	nd	0.8	8.2
Infusion bag Pt 04	0.2	nd	0.2	0.1	1.5
Infusion bag Pt 05	0.3	nd	0.1	0.1	1.3
Infusion bag Pt 06	0.3	0.1	nd	1.2	0.5
Infusion bag Pt 07	0.2	nd	nd	0.1	1.1
Infusion bag Pt 08	0.2	nd	nd	0.1	0.8
Infusion bag Pt 09	0.1	nd	0.1	0.1	1.3
Infusion bag Pt 10	0.4	nd	0.2	0.2	47.8
Infusion bag Pt 11	0.1	nd	0.6	1.3	0.8
Infusion bag Pt 12	0.1	0.1	nd	0.1	0.9
Infusion bag Pt 13	0.3	nd	nd	0.2	1.0
Infusion bag Pt 14	0.5	nd	0.1	0.3	2.3
Infusion bag Pt 15	24.5	nd	nd	0.2	nd
Median ± SD	0.3 ± 6.2	0.2 ± 0.1	0.2 ± 0.2	0.2 ± 0.4	1.1 ± 12.5
	5-FU (pg/cm^2)		5-FU (pg/cm^2)	5-FU (pg/cm^2)	5-FU (pg/cm^2)
Infusion bag 5-FU 01	8.8	nd	nd	nT	3.5
Infusion bag 5-FU 02	0.8	2.0	0.5	nT	10.0
Infusion bag 5-FU 03	1.0	nd	nd	nT	13.0
Infusion bag 5-FU 04	1.5	nd	1.0	nT	nd
Infusion bag 5-FU 05	1.8	nd	nd	nT	nd
Infusion bag 5-FU 06	560.5	nd	0.5	nT	nd
Infusion bag 5-FU 07	5.0	50.8	nd	nT	1.8
Infusion bag 5-FU 08	3.8	nd	nd	nT	nd
Infusion bag 5-FU 09	242.5	2.2	nd	nT	3.8
Infusion bag 5-FU 10	11.5	791.5	nd	nT	nd
Infusion bag 5-FU 11	nd	1.4	8.8	nT	19.5
Infusion bag 5-FU 12	150.8	nd	nd	nT	nd
Infusion bag 5-FU 13	0.5	nd	1.3	nT	10.8
Infusion bag 5-FU 14	24.8	nd	nd	nT	13.8
Infusion bag 5-FU 15	95.5	3.5	0.5	nT	3.5
Median ± SD	6.9 ± 156.4	2.9 ± 318.8	0.8 ± 3.3	nT	10.0 ± 6.0

nd: below detection limit of 0.2 ng 5-FU/sample = 0.5 pg/cm^2; LOD for Pt = 0.02 ng/sample = 0.05 pg/cm^2 nT: not tested, SD: standard deviation.

Syringes

In total 35 syringes were sampled, of which 25 products were wiped after mC and 10 without mC. Only rather low 5-FU concentrations (6 syringes below LOD, max. 3.6 pg/cm^2) were detected on the 10 syringes sampled without manual capping (scenario A). When the manual capping was performed by an experienced operator (scenario C), the 5-FU concentrations measured were also very low (5 syringes below LOD, max. 7.3 pg/cm^2). However, when the manual capping was performed by an inexperienced operator (scenario B), nine out of 15 syringes showed 5-FU contamination ranging from 7.3 to 488 pg/cm^2 (Table 4).

Discussion

Surface contamination is the major route of exposure while handling antineoplastic drugs. In this study,

Table 4: External contamination with 5-fluorouracil during robotic preparation of injection syringes with APOTECAchemo Rev. C. Samples were taken from the outer surface of the syringes (110 cm^2) either without manual capping or with manual capping by an experienced or inexperienced operator.

Type of sample area (110 cm^2 per syringe)	Scenario A, without manual capping	Scenario B, with manual capping by an inexperienced operator	Scenario C, with manual capping by an experienced operator
	5-FU (pg/cm^2)	5-FU (pg/cm^2)	5-FU (pg/cm^2)
Syringe 5-FU 01	1.8	nd	nd
Syringe 5-FU 02	2.7	60.0	3.6
Syringe 5-FU 03	1.8	8.2	2.7
Syringe 5-FU 04	3.6	77.3	nd
Syringe 5-FU 05	nd	nd	nd
Syringe 5-FU 06	nd	8.2	7.3
Syringe 5-FU 07	nd	10.9	nd
Syringe 5-FU 08	nd	nd	2.7
Syringe 5-FU 09	nd	17.3	4.5
Syringe 5-FU 10	nd	nd	nd
Syringe 5-FU 11	nT	7.3	nT
Syringe 5-FU 12	nT	nd	nT
Syringe 5-FU 13	nT	488.2	nT
Syringe 5-FU 14	nT	102.7	nT
Syringe 5-FU 15	nT	nd	nT
Median ± SD	2.1 ± 0.8	17.3 ± 154.7	3.6 ± 1.9

nT: not tested, nd: below detection limit of 0.2 ng 5-FU/sample = 1.8 pg/cm^2.

we present the levels of surface contamination during the preparation of antineoplastic drugs with robotic systems and manual preparation by surface wipe sampling. Wipe sampling was performed in the working area and on the finished test products containing defined amounts of 5-FU or Pt-based antineoplastics in different settings over an interval of six years. Pt and 5FU were chosen because they act next to cyclophosphamide (CP) most often as indicators for occupational hazard in cytotoxic preparation units [5, 6, 8–12]. They represent a high percentage rate of the routine work in cytotoxic preparation units and thereby a high probability of spreading. Moreover, validated sampling strategies and sensitive analytical methods are available [8, 19, 20]. On the other hand, the contamination levels are directly related to the physico-chemical characteristics of the medicinal products used, the sampling strategies, and the sensitivity of the assays [9–12]. In this study, wipe sampling was performed at five different time points (Test 1–5) and different versions of the robotic system. The study design with different time points is not ideal, but there was no other possibility to study the influence of variations of the robotic system over time. Of note, the sampling method, the drugs analysed (Pt, 5-FU), and the analytical techniques remained unchanged over time. Therefore, comparison of the results is justified, while the comparability with results from studies on other terms and conditions is limited. The number of samples taken during the manual process is also limited and sampling during the manual process was not repeated. The reason is, that processes remained unchanged over time. Wipe sampling during manual preparation is done in regular intervals, but results are not reported here because the number of products and the doses are not standardized.

Surface wipe sampling was performed before and after the preparation process on predefined locations in the preparation area prone to a high probability of contamination during the automatic or manual preparation process [9, 11]. These are locations were the vials are punctured, solutions withdrawn, and vials are deposited. Healthcare workers may come into contact with the surfaces during the cleaning procedure and if the robot requires the human intervention during the preparation process due to technical problems. Next to the preparation process, the cleaning procedure and the contamination levels of the finished products were analysed. The latter ones were studied, because the most important fact is, that potentially released antineoplastics remain inside the working areas of the robots and BSCs and do not contaminate the surrounding areas and products.

Environmental wipe samples

Regarding the automated systems, drug residues were mostly detected on the dosing device and on the gripper of the robotic arm. At these locations, the high-levels of contamination can derive from droplets, which may be generated during the withdrawal and injection of the concentrated drug solutions. By using vented needles, the formation of aerosols is considerably diminished. However, droplets may be generated at the tip of the needles, when the needle is withdrawn from the vial stopper and/or the stopper of the infusion bag. Moreover, in these experiments, the preparation of standardized cytotoxic products in series may have increased the probability of droplet formation because of the large number of drug vials handled and the repeated withdrawal and injection cycles operated with the same syringe-needle-device.

The initial environmental monitoring performed with the CytoCare robot showed higher surface contamination levels than the experiments with the upgraded APOTECAchemo Rev. B. This is most probably a consequence of more accurate motion sequence of the robotic arm. Diligent setting of the parameters which control each operation of the robotic arm by experienced technical staff of the provider is crucial to ensure a precise and safe process. However, the contamination of the outer surfaces of the incoming vials can lead to surface contamination inside the working area.

Sessink et al. [11] monitored gloves, vials, infusion bags, and surface contamination with CP inside and outside the CytoCare robot. The robotic system CytoCare enabled the preparation of CP with low levels of environmental and product contamination. They reported that contamination with CP on the outer surface of the partly used or reconstituted vials result in contamination inside and outside the working areas of the robotic system. When Schierl et al. studied the environmental contamination by cyclophosphamide preparation with APOTECAchemo Rev. C [9]. they also found low contamination rates. Contamination with CP was lower during automated preparation than manual preparation.

The Pt and 5-FU concentrations measured in our study before and after preparation ranged in the same order of magnitude. The fact that sometimes lower concentrations were measured after the preparation procedure, indicates that no consistent spillage/contamination occurred during the preparation process. Detected drug residues in samples collected after cleaning (i. e. before preparation of test products) revealed that the experiment did not start in a contamination free environment. The decontamination procedure was not completely effective and it could even result in spread of contamination rather than cleaning. These results are in line with the results of other studies were contamination levels before and after cleaning of the BSC or robotic systems were measured [9, 11, 12]. Hagebeucker et al. [12] recently monitored the level of surface contamination with nine different antineoplastic drugs inside APOTECAchemo Rev. C. during the installation qualification. The most critical locations (i. e. gripper of the robotic arm, surface beneath the robotic arm, infusion bag clamps, shelves) were sampled before and after the cleaning procedure. Only in few cases contamination got obvious. Minor contamination with Pt was reduced by the cleaning procedure with alkaline cleaning solution. Even by using highly effective cleaning agents surface contamination is not completely eliminated but reduced in a magnitude of 99.5 %. Therefore, residual amounts of drug remain on the surfaces and drug accumulation cannot be excluded [23–25]. Studies focused on the most appropriate cleaning procedure of the working areas of the robotic system are encouraged. Of note, contamination of the horizontal surfaces inside the working area can be prevented by covering with single-use preparation mats.

During manual preparation the highest contamination levels were measured on the preparation mat and on the gloves worn by the pharmacy technician. Contamination can be generated from spillage while transferring the drug solution. Indeed, the overall highest drug contaminations detected in the wipe samples (i. e. 1,250,000 pg/cm^2 of 5-FU in CytoCare and 1,725,000 pg/cm^2 of 5-FU in BSC) were most likely caused by releasing a droplet of concentrated 5-FU solution during the preparation process. Contamination can also derive from outer surfaces of the drug vials delivered from the manufacturers [26]. If the vials are not cleaned by wiping, as it is the case in our setting, they pose a contamination risk. The vials are stored on a mat to avoid contamination of the working surface area of the BSC and to facilitate the decontamination and cleaning procedures. In addition, the outer gloves are routinely changed every 15 minutes.

However, comparability of the study results is limited due to the variability of methodologies and working procedures tested. The threshold guidance values (TGVs), proposed by Schierl et al. [27], allow a benchmark of the actual contamination levels in comparison to a large sample of manual cytotoxic preparation units, but robotic systems are not included. A guidance value for cytotoxic robots could be an efficient tool to benchmark the occupational exposure to antineoplastics drugs.

Wipe samples from the outer surfaces of the finished products

Surface contamination of the finished products (infusion bags, syringes) bears the risk of spreading hazardous antineoplastics in the centralized preparation unit and even in the administration areas. Minimal surface contamination on the finished products reduces the risk for all healthcare workers.

The analysis of the infusion bags revealed that the presence of cytotoxic residues varied depending on the robotic system as well as the type of preparation. The infusion bags prepared with CytoCare were more frequently and with higher concentrations of 5-FU contaminated than the infusion bags prepared with the APOTECAchemo Rev. B. Contaminations with Pt on infusion bags were minimal during automated preparation and higher during manual preparation. Iwamoto et al. [10] measured the contamination levels with CP and 5-FU during manual and automated preparation. Gloves and infusion bags were less contaminated with CP and 5-FU during compounding with APOTECAchemo Rev. C than during manual preparation. During manual preparation contamination can arise from the contaminated gloves of the pharmacy technicians and the mat where the bags are deposited. In contrast, the infusion bags never get in direct contact with potentially contaminated surfaces in the working area of the robotic systems.

There is a higher probability of outer surface contamination during automated preparation when syringes are used as primary packaging material. Therefore, we studied the surface contamination of syringes filled with 5-FU by the recently installed APOTECAchemo Rev. C in detail. The outer surfaces of syringes get into direct contact with potentially contaminated components of the robotic system. They are handled by the gripper of the robotic arm and placed in the dosing device for the withdrawal of drug solution. In addition, the preparation of syringes is not fully automated. The syringes are to be manually capped in the loading area of the robot. De-connecting the needle device and expelling air from filled syringes can cause leakage of drug solution followed by contamination of the operator's gloves and can be further spread to whatever is touched. Different case scenarios investigated, suggested that the surface contamination of syringes did not derive from the automated part of the preparation procedure but from the manual capping procedure performed by the operator in charge. The magnitude of the residues detected was random, independent from the order of filling, making it unlikely that the contamination derived from the preparation process especially because the syringes handed out by the robot revealed only negligible traces of 5-FU. Furthermore, the correlation between the contamination level or frequency and the operator was evaluated. The results highlighted that the proper working technique of a trained operator with a practiced hand plays a crucial role and can considerably reduce the contamination risk. However, the confinement of this critical procedure inside the working area of the robotic system is encouraged in future technical developments. Moreover, the fully automatic preparation of syringes would be more efficient than the semi-automatic or fully manual preparation and thereby favour the preparation of syringes by a robotic system.

Conclusions

Surface wipe sampling during automated preparation of Pt and 5-FU infusion bags and syringes with different versions of a robotic system revealed varying contamination levels inside the working area and on the outer surfaces of finished products. However, the risk of contamination remained mostly localised inside the working area of the robotic system. Even with a robotic system, spillages cannot be avoided at any time and are not removable in total by the decontamination and cleaning procedure. Optimum cleaning procedures are to be further investigated. Infusion bags prepared with the robotic system are less contaminated with antineoplastics on the outer surface than manually prepared infusion bags. Filling syringes with APOTECAchemo ensures marginal contamination on the outer surfaces, but the manual capping procedure bears a risk for noticeable surface contamination depending on the operator's experience.

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