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Short Communication

Multicomponent high-performance liquid chromatography/tandem mass spectrometry analysis of ten chemotherapeutic drugs in wipe samples☆

Shinichiro Maeda[a,b,*], Yoshihiro Miwa[a]

[a] Department of Pharmacy, Osaka University Hospital, Osaka, Japan
[b] Graduate School of Pharmaceutical Sciences, Osaka University, Osaka, Japan

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ABSTRACT

Progress in chemotherapy leads to increased numbers and variety of chemotherapeutic drugs, and multicomponent analysis of these drugs is a necessary step. We used liquid chromatography–tandem mass spectrometry and developed a multicomponent analysis of ten drugs used in chemotherapy: vindesine, vincristine, vinblastine, doxorubicin, epirubicin, ifosfamide, cyclophosphamide, irinotecan, docetaxel, and paclitaxel. We selected five internal standards for each category of drug, because the ionization efficiencies of product ions varied widely. The total run time was 22 min, applying a gradient elution of water and acetonitrile in the presence of 0.1% formic acid. The lower limit of quantification was 50 ng/wipe samples for vindesine, vincristine, and vinblastine, and 5 ng/wipe samples for the remaining seven drugs. Accuracy (88.6–112.9%, 85.2–111.7%) and precision (1.0–11.5%CV, 3.6–14.4%CV) in within-run and between-run assays of QC solutions were acceptable. Without outliers, in within-run and between-run assays of QC samples, accuracy was 90.6–113.9% and 91.1–130.4%, respectively, and precision was 2.2–19.0%CV and 4.8–14.9%CV, respectively. Accuracy and precision of High QC samples of irinotecan were deviated. Our analysis procedure has sufficient sensitivity and is convenient enough for regular monitoring.

1. Introduction

Recently, progress in chemotherapy has led to increased numbers and variety of chemotherapeutic drugs, and significant numbers of cancer patients have received chemotherapy in both ambulatory and hospital settings. At the same time, many healthcare workers expressed concern regarding the risk of occupational exposure to hazardous drugs.

Tomioka and Kumagai [1] monitored occupational exposure to chemotherapeutic drugs, reporting on routes of exposure and the levels at which the drugs exert their effects. Specifically, they described: (i) external exposure, including exposure to airborne drugs and those deposited on work surfaces; (ii) internal exposure, such as the presence of drugs or their metabolites in blood and urine; (iii) cellular level effects, including the presence of mutagens in urine and the frequency of sister chromatid exchanges; and (iv) effects at the individual level, including susceptibility to cancer and effects on reproduction. Recent improvements in analytical instruments have permitted direct investigation of external and internal exposure.

Monitoring of specific drugs was performed in internal and external exposure studies [2–6], and detected amounts of platinum compounds (cisplatin, carboplatin, and oxaliplatin), 5-fluorouracil [7], and cyclophosphamide [8] were used as a reference values in several countries.

In accordance with increasing chemotherapeutic drug use, multicomponent analysis of hazardous drugs in the workspace is required. There are relatively few reports of occupational exposure in healthcare workers [9–15].

In present study, we used liquid chromatography–mass spectrometry/mass spectrometry (LC–MS/MS) and developed multicomponent analysis procedures for chemotherapeutic drugs. We selected ten drugs that are commonly used in chemotherapy. These included three vincalkaloid drugs (vindesine, vincristine, and vinblastine), two anthracycline drugs (doxorubicin and epirubicin), two alkylating agents (ifosfamide and cyclophosphamide), one camptothecin derivative (irinotecan), and two taxane drugs (docetaxel and paclitaxel). Internal standards were selected according to each category of drug. The structure and exact mass of each drug and internal standard are shown in Table 1.

☆ The name of the English checker is "Honyaku Center Inc.".

* Corresponding author at: Department of Pharmacy, Osaka University Hospital, 2-15 Yamadaoka, Suita, Osaka 565-0871, Japan. Tel.: +81 6 6879 3372; fax: +81 6 6879 3379.
E-mail addresses: maeda313@hosp.med.osaka-u.ac.jp, maeda313@phs.osaka-u.ac.jp (S. Maeda).

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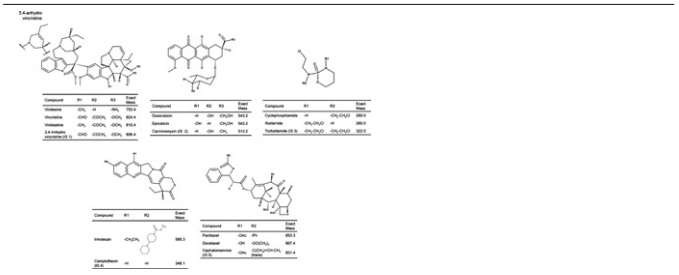
Table 1
Structure and exact mass of each drug and internal standard (IS).



2. Materials and methods

2.1. Chemicals and materials

Doxorubicin, ifosfamide, cyclophosphamide and paclitaxel were purchased from Wako Pure Chemical (Osaka, Japan). 3,4-Anhydro vincristine, used as internal standard (IS) 1, was purchased from Toronto Research Chemicals (Toronto, Canada). Docetaxel, carminomycin (used as IS 2), and trofosfamide (used as IS 3) were purchased from Santa Cruz Biotechnology (California, USA). Camptothecin, used as IS 4, was purchased from Tokyo Chemical Industry (Tokyo, Japan). Irinotecan and cephalomannine (used as IS 5) were purchased from Sigma–Aldrich (Missouri, USA). Vincristine, vinblastine and epirubicin were kindly provided by Nippon Kayaku. Vindesine was kindly provided by Shionogi. Acetonitrile and methanol (LC–MS chromasolv) were also purchased from Sigma–Aldrich (Missouri, USA), and formic acid was purchased from Wako Pure Chemicals.

2.2. Chromatographic conditions

An Alliance 2695 HPLC separation module (Waters; MA, USA) with PDA detector, cooled autosampler and column oven was used to perform this study. Chromatographic separation was achieved on an octadecyl silyl column (Inertsil® ODS-3; 50 mm × 2.1 mm; particle size, 3 μm; GL Sciences, Tokyo, Japan) with a guard column (cartridge guard-column E®; 20 mm × 2.0 mm; particle size, 3 μm, GL Sciences, Tokyo, Japan). The column oven was maintained at 30 °C and the autosampler was maintained at 5 °C. The mobile phases consisted of 0.1% formic acid–water (mobile phase A) and acetonitrile (mobile phase B). The flow rate was 0.3 ml/min and gradient elution was performed in the following manner: 15% of mobile phase B to 45% over 10 min; 45% of mobile phase B to 80% over 7 min. Subsequently, the concentration of mobile phase B was linearly decreased to 15% for 1 min and equilibrated for 4 min. Total run time was 22 min.

2.3. Mass spectrometry conditions

A tandem quadrupole MS TQD (Waters; MA, USA), operated in multiple reaction monitoring (MRM) and positive electrospray ionization (ESI) mode, was used for detection and MassLynx 4.1 software was used for data acquisition and processing. MS/MS parameters (precursor ion, product ion, cone energy, collision energy and retention time) of each drug were individually optimized by QuanOptimize software and syringe pump infusion in primary mobile phase by constant flow.

2.4. Preparation of stock solutions and working solutions

Vindesine was prepared in a solution of 0.1% formic acid–water to obtain a concentration of 2 mg/ml. Camptothecin and other drugs were prepared in a solution of 0.1% formic acid–methanol to obtain a concentration of 100 μg/ml and 2 mg/ml, respectively. Aliquots of these solutions were stored at −80 °C, then diluted in 0.1% formic acid–methanol to obtain a final concentration of 100 μg/ml of each stock solution and stored at −30 °C.

Stock solutions of the three vincalkaloids were mixed to form working solutions, containing 33.3 μg/ml of vindesine, vincristine, and vinblastine, respectively. Stock solutions of the other seven drugs were also mixed and diluted in 0.1% formic acid–methanol to working solutions, containing 5 μg/ml of doxorubicin, epirubicin, ifosfamide, cyclophosphamide, irinotecan, docetaxel, and paclitaxel, respectively. The working solutions of the internal standard mixtures were prepared by dissolving 100 μg/ml of 3,4-anhydro vincristine, and dissolving 10 μg/ml of carminomycin, trofosfamide, camptothecin, and cephalomannine, respectively. For each daily analysis, these working solutions were freshly prepared from stock solutions, and stored at −30 °C.

We used black Eppendorf tubes for stock solutions of anthracycline and vincalkaloid drugs, and for all working solutions.

2.5. Preparation of calibration standards and quality control (QC) samples

The calibration standards and quality control (QC) samples were prepared as working solutions. We used the following levels for calibration standards: 0, 5, 10, 20, 30, 50, 100, 200, 500, 1000 ng/mL and equivalent concentrations to wipe samples for the three vincalkaloids drugs, and 0, 0.5, 1, 2, 3, 5, 10, 20, 50, 100 ng/mL and equivalent concentrations to wipe samples for the other seven drugs.

QC samples were obtained at concentrations of 750 and 75 ng/mL, and equivalent concentrations to wipe samples, for the three vincalkaloids drugs and the other seven drugs, respectively (high QC), at 100 and 10 ng/mL, and equivalent concentrations to wipe samples, respectively (medium QC), and at 30 and 3 ng/mL, and equivalent concentrations to wipe samples, respectively (low QC).

2.6. Sample processing

The extraction of wipe samples for environmental assessment was a modified version of the method described in our previous report [6]. Briefly, we first applied internal standard mixtures, containing 10 μg of 3,4-anhydro vincristine, 500 ng of carminomycin, trofosfamide, camptothecin, and cephalomannine to the surfaces of sampling areas. After these areas were air-dried, we wiped an 800 cm^2 area (20 cm × 40 cm) with a Kimwipe® S-200 (120 mm × 215 mm, Nippon Paper Crecia, Tokyo, Japan) wetted with 1 ml of 0.1% formic acid–70% methanol. We repeated the wiping operation twice, then placed both sheets in light-blocking polypropylene conical tubes and added 8 ml of 0.1% formic acid–70% methanol. We shook the tubes for 30 min at 2000 rotations per min. Extracts were then directly injected into the LC–MS/MS equipment without dilution.

2.7. Validation procedures

Validation of the assay were separately performed for the sampling procedure (QC solutions) and for the whole laboratory method, included wiping and extracting procedures (QC samples), in accordance with the FDA Guidance for Industry on Bioanalytical Methods Validation [16] and The European Medicines Agency (EMA) Guideline on Bioanalytical Method Validation [17].

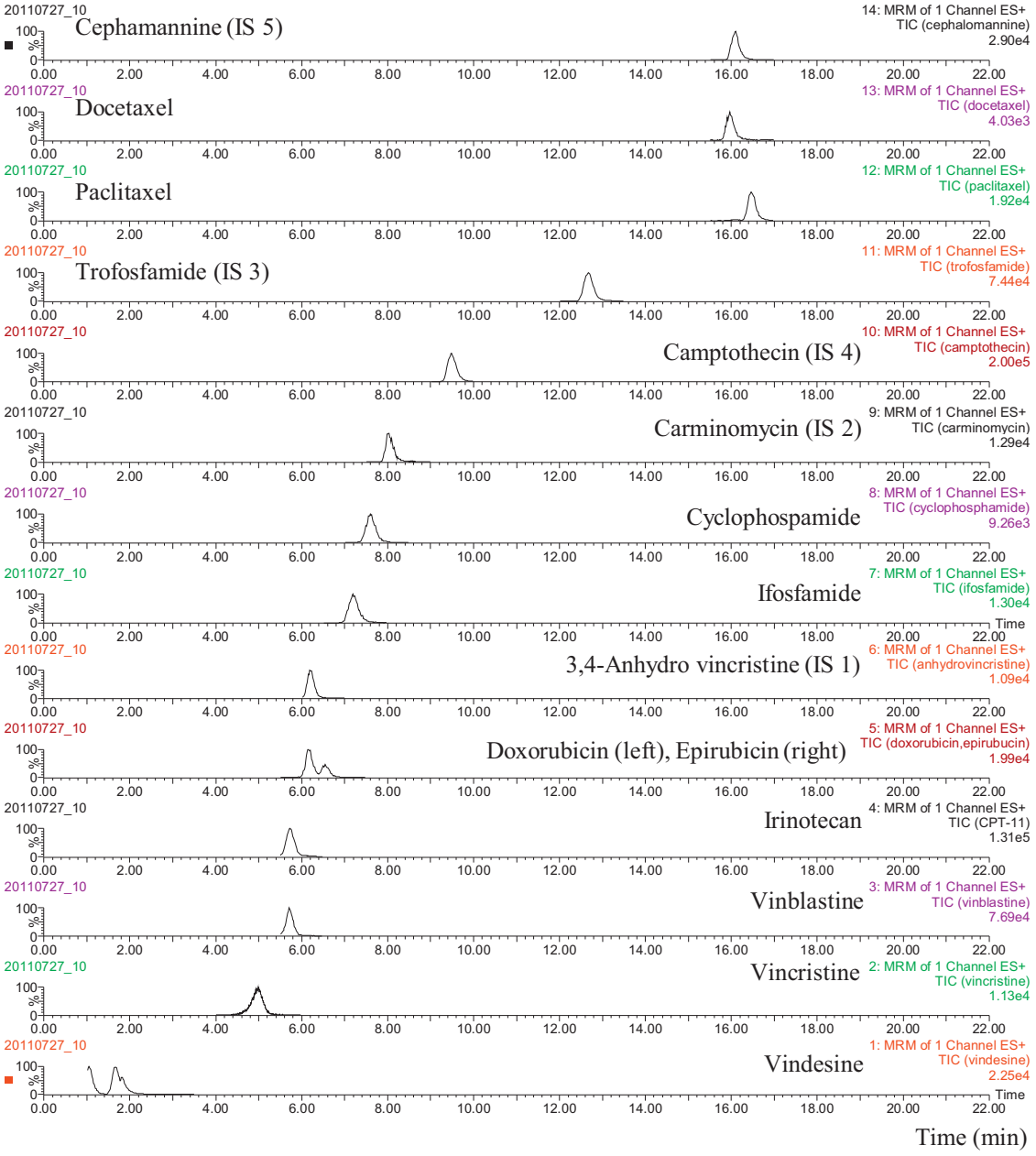


Fig. 1. Typical chromatograms of the calibration standard sample containing ten different chemotherapeutic drugs and five internal standards (IS).

Calibration standards were prepared and analyzed in 3 replicates in 3 independent runs. In order to obtain acceptable linearity, deviations from the mean concentration calculated over 3 runs were required to be within ±15% of nominal concentrations for the non-zero calibration standards, except for the lower limit of quantification (LLOQ) level where a deviation of ±20% was allowed.

In the within-run assay, accuracy and precision were determined by analyzing five replicates of QC samples at each concentration for a single assay. In the between-run assay, these were determined by analyzing five QC samples per day at each concentration on 3 different days. In within-run assay and between-run assay, accuracy was calculated as the percent deviation from the nominal concentration and was required to be within ±15%, while precision was expressed as the coefficient of variation (CV) at each QC concentration and could not exceed ±15%.

3. Results

3.1. Chromatographic conditions and mass spectrometry conditions

All drugs were clearly detected over a total run time of 22 min. A typical chromatogram of each drug and internal standard are shown in Fig. 1. The tandem quadrupole instrument was determined to have sufficient sensitivity. The optimized parameters of MS/MS conditions are summarized in Table 2. The molecular ion $[M+H]^+$ of each drug was selected as a precursor ion, and an abundant fragment ion was selected as a product ion.

3.2. Validation procedures

Different regression models were tested using Akaike's information criterion [18] to determine the best calibration curves for all

Table 2
Parameters of MS/MS conditions.

Parameters compounds	Precersor ion	Product ion	Cone energy (V)	Collision energy (V)	Retention time (min)
Vindesine	754.5	124.2	55	50	1.65
Vincristine	825.4	765.6	70	40	5.02
Vinblastine	811.4	224.1	60	45	5.75
3,4-Anhydro vincristine (IS 1)	807.4	747.5	65	30	6.22
Doxorubicin	544.5	397.2	20	12	6.18
Epirubicin	544.5	397.2	20	12	6.60
Carminomycin (IS 2)	514.2	307.2	20	25	8.29
Ifosfamide	261.0	153.9	45	25	7.21
Cyclophosphamide	261.0	140.3	45	30	7.63
Trofosfamide (IS 3)	323.1	153.9	30	25	12.69
Irinotecan	587.7	167.3	60	45	5.77
Camptothecin (IS 4)	349.1	305.2	50	25	9.51
Docetaxel	808.8	226.1	20	14	15.95
Paclitaxel	854.8	286.3	25	24	16.48
Cephalomannine (IS 5)	832.8	264.2	25	20	16.09

drugs. Weighted linear regression models with a weight equal to $1/x^2$ gave the best quantitative performance in the studied concentration range for all drugs, with the exception of vincristine and vinblastine. Quadratic regression models with a weight equal to $1/x^2$ gave the best quantitative performance for vincristine and vinblastine.

A reproducible relationship between concentration and response was found over the measured concentration range for all drugs. Mean calculated concentrations over 3 runs did not deviate by more than ±15% from nominal concentrations for the non-zero calibration standards. The calibration curves were fitted over a range of 5–1000 ng/wipe samples for doxorubicin, epirubicin, ifosfamide, cyclophosphamide, irinotecan, docetaxel, and paclitaxel, and 50–10,000 ng/wipe samples for vindesine, vincristine, and vinblastine, respectively.

The results of QC solutions and QC samples, assured at three QC concentrations, are summarized in Table 3. Unfortunately, in the QC samples, one of each of the High QC and Medium QC samples showed extremely deviated values, and thus we analyzed the accuracy and precision with and without the outliers. Accuracy and precision of High QC samples for irinotecan were exceeded ±15%.

4. Discussion

In this paper, we described the development of a multicomponent analysis of ten chemotherapeutic drugs assessed using wipe samples. The analyzed drugs are commonly used in chemotherapy and are members of five categories; vincalkaloid drugs, anthracycline drugs, alkylating agents, camptothecin derivatives, and taxane drugs. Since the ionization efficiencies of product ions varied widely and we will extend this analysis method to urine samples and blood samples, we selected five internal standards from each category of drug. That is, 3,4-anhydrovincristine (IS 1) was used as the internal standard for the vincalkaloid drugs, carminomycin (IS 2) was used for anthracycline drugs, trofosfamide (IS 3) was used for alkylating drugs, camptothecin (IS 4) was used for camptothecin derivatives, and cephalomannine (IS 5) was used for the taxane drugs. Response of analyzed drugs and corresponding internal standards were similar, and using internal standards were suitable to correct ionization efficiencies.

Anthracycline drugs are light sensitive and adsorb onto glass containers [19]. Thus, black Eppendorf tubes were used for stock solutions, and light-blocking polypropylene tubes were used during extraction. Only brown glass vials were used in the autosampler. All stock and secondary solutions were aliquoted and stored at −30 °C, and were thawed only once before use.

Because vincalkaloid drugs have distinguishing indole–indoline structures, a basic mobile phase was well-suited for positive ionization [20], and therefore these drugs had a lower incidence of collision-induced dissociation [21]. In addition, vincalkaloid drugs were absorbed on some materials of tubes [22]. For these reasons, the LLOQs of the vincalkaloid drugs were higher than the other drugs and quadratic regression models provided a better fit than linear regression models for vincristine and vinblastine in our tandem MS conditions.

The reason that some QC samples showed extremely deviated values for the QC assay was obviously due to improper application of the internal standard mixtures. With the outliers removed, the accuracy and precision of within-run and between-run assays were within ±15% for all drugs in the three concentrations of QC samples, except for the High QC sample of irinotecan. Although it is uncertain why these values significantly deviated only in the High QC sample of irinotecan, we presumed that the pH of the mobile phase and stock solutions might have been affected. In solution, the lactone ring of irinotecan is in equilibrium with the open-ring carboxylate form, and mobile phase pH and solution concentration can significantly distort its analysis [23–25]. The deviation of the High QC irinotecan sample was unfortunate, however, an analysis in the low concentration range is potentially more relevant to occupational exposure studies [26].

Although the degree of external exposure to hazardous drugs is not directly correlated with internal exposure, keeping environmental contamination low levels is cardinal, because dermal penetration and inhalation are presumed to be the main route of internal exposure [27]. Previously, we focused on occupational exposure to epirubicin [5], cyclophosphamide and ifosfamide [6], and reported that external exposure to these drugs did not necessarily result in internal exposure.

Detected amounts of hazardous drugs [7,8] were used as a reference value of occupational exposures in several countries. In Japan, countermeasures to occupational exposures of healthcare workers were lagged behind, and multicomponent external occupational exposures studies were required.

We have already adapted our multicomponent analysis procedure to external exposure studies, and the results were summarized in Table 4 [26]. We collected wiping samples from the surfaces of the biological safety cabinets and from the surfaces of the tables inside/outside a separated area, and revealed that unexpected environmental contaminations had occasionally occurred in our hospital. Our developed procedure has sufficient sensitivity for external exposure studies, and is convenient enough for regular monitoring.

Table 3
Accuracy and precision of within-run and between-run assays for the QC solutions (the upper) and QC samples (the lower). In the within-run assay, 5 replicates were performed for a single assay, and for the between-run assay, measurements were performed on 3 different days with 5 replicates per day.

Compounds	Nominal conc	Within-run		Between-run		Compounds	Nominal conc	Within-run		Between-run	
		Accuracy (%)	Precision (%CV)	Accuracy (%)	Precision (%CV)			Accuracy (%)	Precision (%CV)	Accuracy (%)	Precision (%CV)
Vindesine	High QC	97.5	4.7	100.3	6.4	Ifosfamide	High QC	106.3	1.5	108.2	3.6
	Medium QC	96.4	3.9	100.5	12.2		Medium QC	98.8	5.3	109.1	11.4
	Low QC	88.6	11.5	87.3	14.4		Low QC	96.0	4.5	102.2	8.5
Vincristine	High QC	105.8	2.7	100.8	11.4	Cyclophosphamide	High QC	102.6	1.0	106.4	5.1
	Medium QC	103.0	6.4	95.8	10.7		Medium QC	105.0	5.3	102.9	8.7
	Low QC	112.9	6.9	102.0	13.4		Low QC	94.0	5.3	92.2	9.0
Vinblastine	High QC	101.6	5.2	103.5	5.8	Irinotecan	High QC	109.6	1.6	105.9	11.1
	Medium QC	103.7	6.0	103.6	12.4		Medium QC	100.0	4.9	98.5	11.8
	Low QC	98.1	8.7	104.1	14.2		Low QC	94.7	5.9	94.5	11.0
Doxorubicin	High QC	107.4	2.0	99.7	11.0	Docetaxel	High QC	104.7	4.4	111.7	6.5
	Medium QC	97.8	5.5	93.9	12.4		Medium QC	101.8	4.4	106.4	11.1
	Low QC	90.7	4.0	85.2	7.3		Low QC	100.1	8.4	99.0	13.8
Epirubicin	High QC	109.7	2.1	110.6	12.1	Paclitaxel	High QC	99.4	1.5	100.3	10.2
	Medium QC	102.0	4.0	94.8	10.3		Medium QC	97.0	2.2	99.9	7.6
	Low QC	101.3	2.9	97.0	14.0		Low QC	96.7	6.5	99.1	8.5

Compounds	Nominal conc	Within-run		Between-run		Compounds	Nominx'l conc	Within-run		Between-run	
		accuracy (%)	precision (%CV)	accuracy (%) [without outlier]	precision (%CV) [without outlier]			Accuracy (%)	Precision (%CV)	Accuracy (%) [without outlier]	Precision (%CV) [without outlier]
Vindesine	High QC	102.9	4.9	102.4	6.1		High QC	105.1	2.2	113.8 [108.4]	113.8 19.1
	Medium QC	93.9	5.0	99.0	13.1	Ifosfamide	Medium QC	103.2	3.6	94.2 [97.0]	94.2 14.5
	Low QC	90.6	5.2	100.4	13.1		Low QC	92.2	4.2	97.8	97.8 10.9
Vincristine	High QC	105.4	2.4	98.6	6.7		High QC	107.4	3.1	108.3 [103.8]	108.3 17.8
	Medium QC	104.5	4.1	96.3	9.0	Cyclophosphamide	Medium QC	102.1	6.4	92.3 [93.4]	92.3 11.2
	Low QC	113.9	7.7	98.6	14.6		Low QC	102.6	3.8	97.6	97.6 10.4
Vinblastine	High QC	107.0	2.7	99.5	8.7		High QC	115.2	19.0	132.0 [130.4]	132.0 15.0
	Medium QC	97.4	4.4	95.2	4.8	Irinotecan	Medium QC	104.6	6.6	91.6 [95.0]	91.6 20.2
	Low QC	97.7	3.8	91.1	10.9		Low QC	97.4	8.2	92.3	92.3 16.7
Doxorubicin	High QC	106.2	3.9	112.1	23.8 [6.5]		High QC	94.5	2.6	107.4 [102.0]	107.4 20.6
	Medium QC	106.9	7.8	99.8	15.7 [10.9]	Docetaxel	Medium QC	108.0	8.0	96.7 [98.8]	96.7 14.9
	Low QC	98.6	3.7	103.8	7.3		Low QC	103.6	7.6	101.9	101.9 10.6
Epirubicin	High QC	110.3	2.6	118.4	25.4 [6.2]		High QC	95.8	3.2	103.5 [98.5]	103.5 19.3
	Medium QC	110.7	9.8	103.2	15.5 [11.9]	Paclitaxel	Medium QC	104.2	4.5	96.7 [98.9]	96.7 11.7
	Low QC	96.4	6.4	97.3	13.9		Low QC	101.5	2.5	102.9	102.9 8.8

Table 4
Frequencies and amounts of drugs detected in wipe samples.

Sampling spots	(A) Surfaces of the biological safety cabinets		(B) Surfaces of the working tables inside a separated area		(C) Surfaces of the working tables outside a separated area	
Compounds	Positive samples (n = 28)	Amounts (ng/wipe)	Positive samples (n = 14)	Amounts (ng/wipe)	Positive samples (n = 28)	Amounts (ng/wipe)
Vindesine	0	–	0	–	0	–
Vincristine	0	–	0	–	0	–
Vinblastine	0	–	0	–	0	–
Doxorubicin	5	7–114	0	–	0	–
Epirubicin	0	–	0	–	0	–
Ifosfamide	0	–	1	7	0	–
Cyclophosphamide	9	5–68	1	21	1	7
Irinotecan	0	–	0	–	0	–
Docetaxel	3	9–348	0	–	0	–
Paclitaxel	1	19	1	14	0	–

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