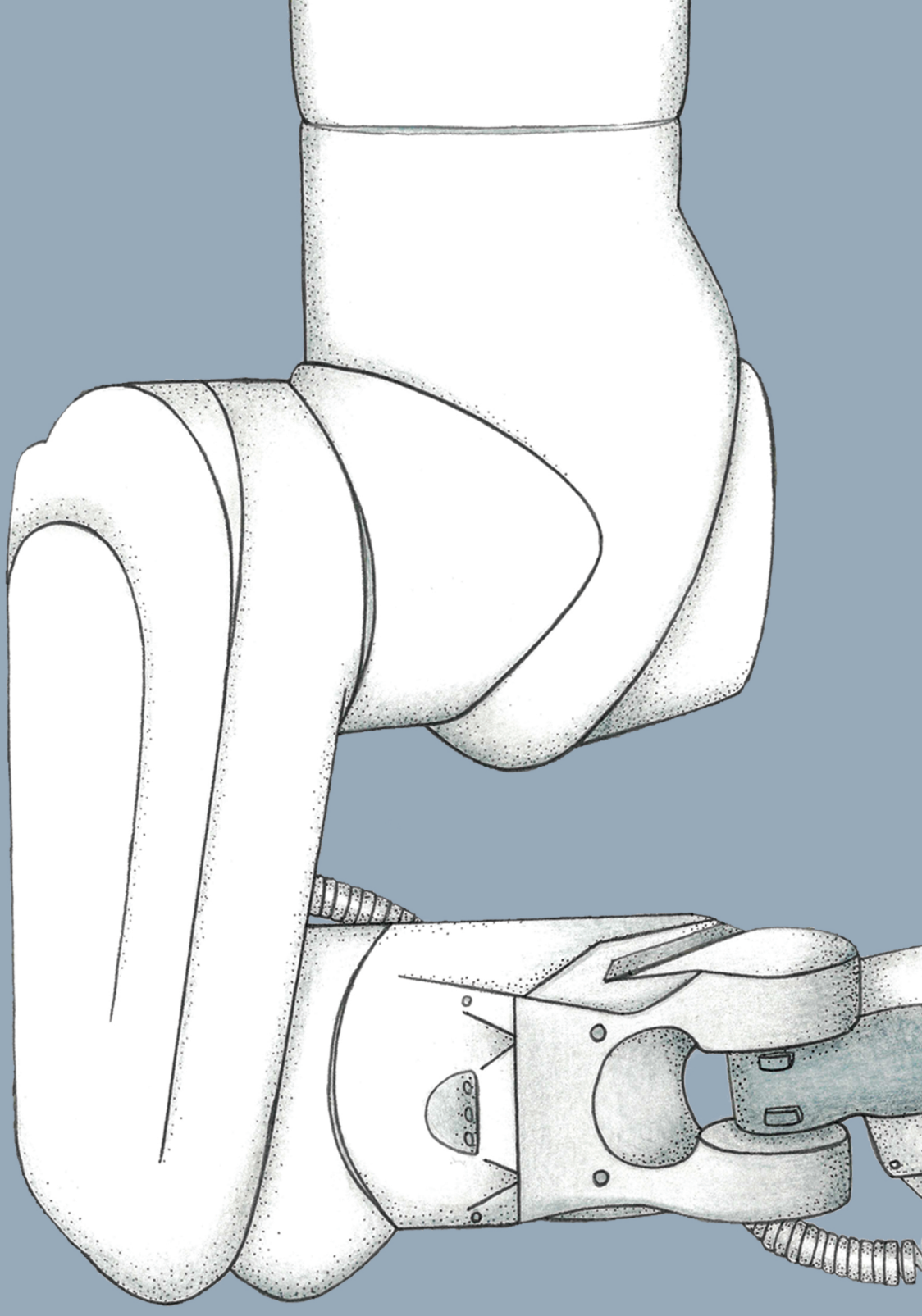
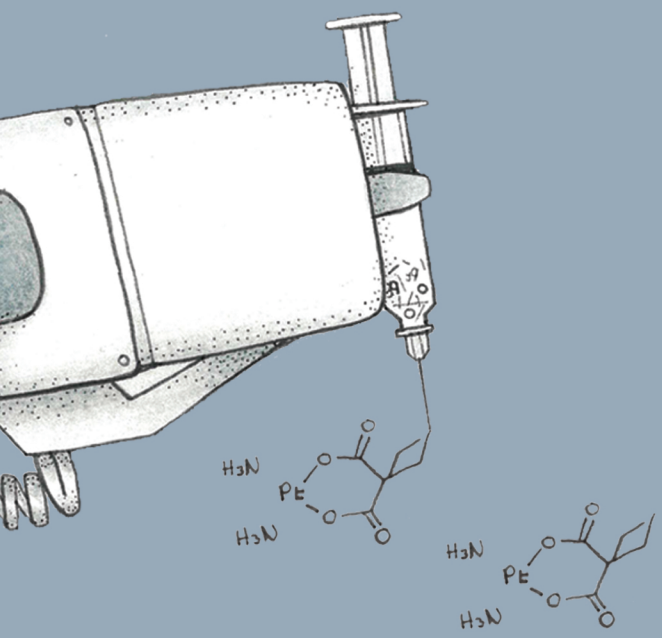
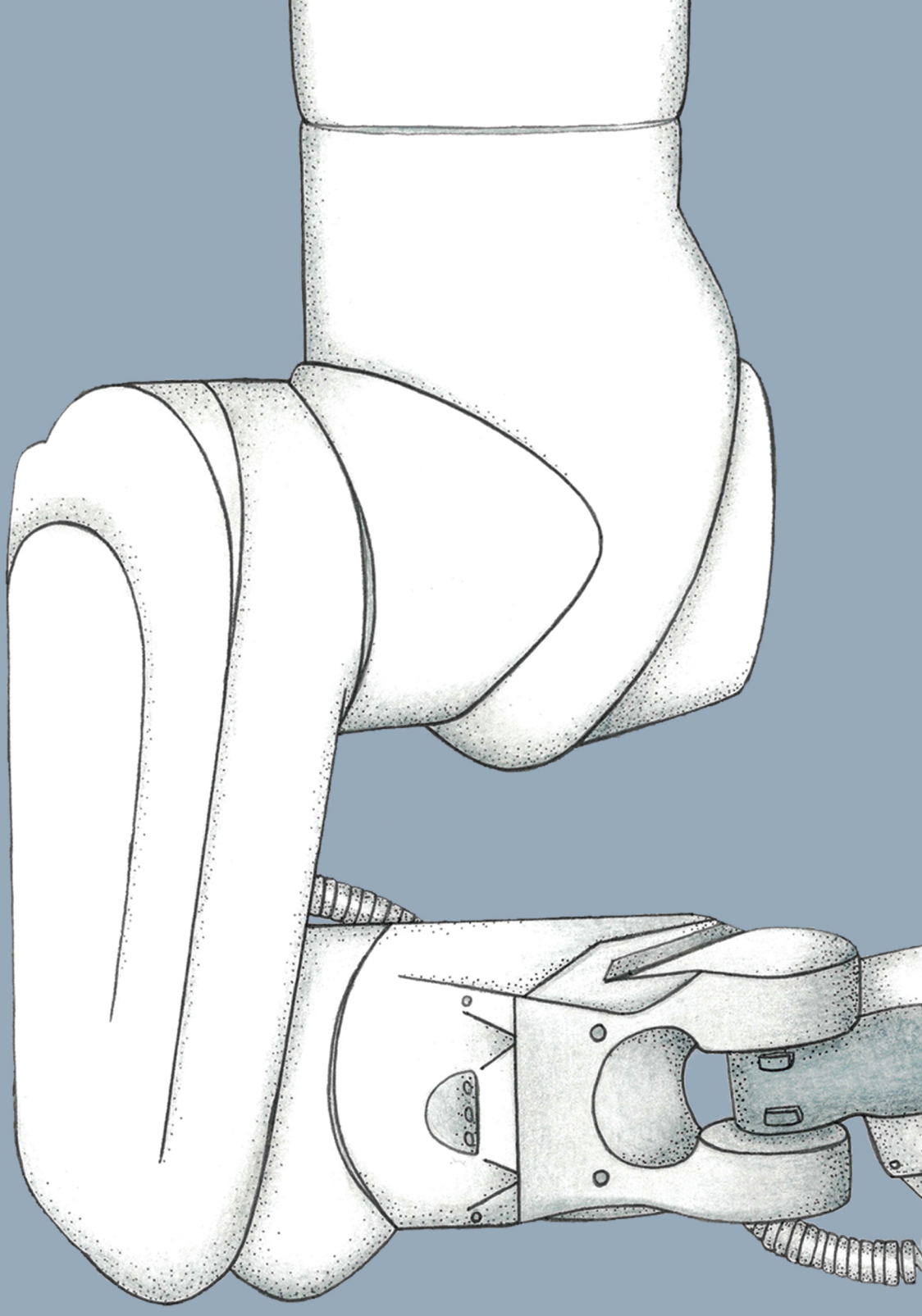


Section II

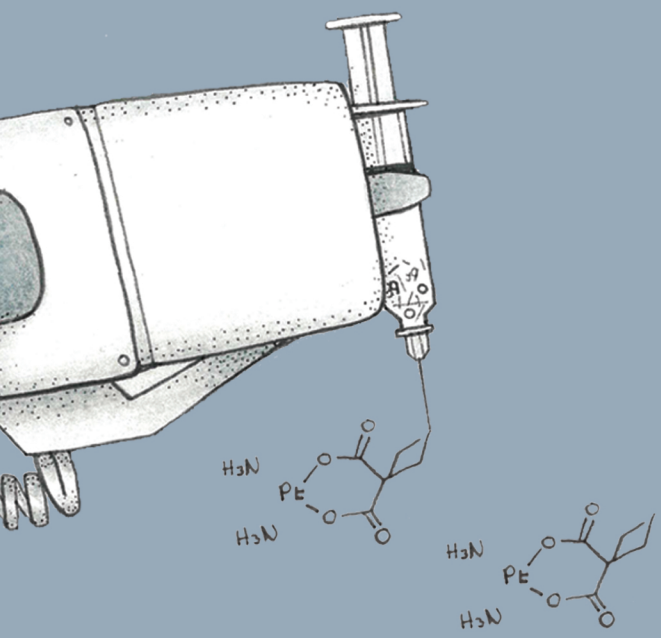
Robotic reconstitution and product quality





2

Robotic compounding versus manual compounding of chemotherapy: Comparing dosing accuracy and precision



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ABSTRACT

Background Cytostatic drugs are increasingly being prepared with a cytostatic robot, though it is not known whether the dose of the final product is more accurate after automated or manual preparation. This study is the first to compare accuracy and precision of automated preparations with manual preparations by measuring volumes and drug concentrations.

Methods The accuracy and precision of automated and manual preparations were compared by gravimetric and concentration measurements. During ten days 80 solutions were prepared; 40 robot preparations and 40 manual preparations. With both preparation methods, 20 methotrexate (MTX) and 20 cyclophosphamide (CP) bags were compounded. We simulated normal working conditions by performing the preparations on Monday till Friday. The MTX and CP concentrations were measured with validated ultra high performance liquid chromatography (UHPLC) methods on the last preparation day.

Results With UHPLC analysis, dose accuracy (mean dose error) of robotic or manual preparation of MTX were 1.70% and 0.96% respectively. With gravimetric analysis, these values were 0.50% and 1.96%. Precision (standard error) of the robotic preparation for MTX was significantly smaller than that of manual preparation ($p < 0.001$).

Dose accuracy (mean dose error) of robotic or manual preparation of CP, with UHPLC analysis, were 6.10% and 5.20% respectively. With gravimetric analysis, these values were 0.67% and 0.18%.

Conclusion We conclude that both robotic and manual compounding produce accurate cytostatic products in which the mean percentage of active substance differs by less than 10% from the prescribed amount. Both preparation methods are compliant with the Dutch Medicines Act and the European Pharmacopoeia.

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INTRODUCTION

Cytostatic drugs are increasingly being prepared with a cytostatic robot, though it is not known whether the dose of the final product is more accurate after automated or manual preparation. Last decade, several automated robots for preparation of chemotherapy admixtures were introduced in hospital pharmacies to improve the safety of medication compounding and to shield hospital pharmacy staff from exposure to hazardous drugs.[1-4] Purchasing a cytostatic robot is a major investment for hospital pharmacies. Therefore it is mandatory to compare the quality of the automated and the manual preparation process.

In general, preparation of ready-to-administer (RTA) cytotoxic drugs is performed manually by trained pharmacy staff in biological safety cabinets (BSC) or isolators with laminar airflow. Manual preparation usually involves a volumetric method. This process requires manual handling by two technicians and is prone to human error. In contrast, automated preparation is based on weighing, which is called gravimetric preparation.[5]

In 2016 OLVG hospital purchased a cytotoxic compounding robot (APOTECAchemo, Loccioni, Italy). The major aim was to improve the working condition for our technicians by reduction of repetitive movements in aseptic procedures. Furthermore, the goal was to minimize the number of full-time technicians needed for the routine cytostatic process, since there was a shortage of qualified technicians in the Amsterdam region. Additional aims were to reduce the possibility of drug errors due to preparation errors by minimizing the human factor during preparation. An example is the introduced automated rejection of final products wherein the amount of active substance differs by more than 10% from the prescribed amount. Finally, automated preparation may reduce exposure of technicians to traces of cytostatic drugs.[6]

Until now, four prior studies with different types of cytostatic robots have compared the accuracy of manual and robotic compounding by weighing the final vehicles.[7-10] Iwamoto et al concluded that robotic preparation was more accurate and precise than manual preparation. Amodeo et al concluded that robotic preparation of cytostatics was more precise than manual preparation, and Seger et al found improved accuracy of prepared chemotherapy and adjuvants by robotic compounding.[8,10] Thus far, no actual drug concentrations were measured in these studies, which means that not the actual prepared doses of automated preparations were compared to manual preparations. More specifically, factors like the accuracy of reconstitution of drugs in powdered form was not included in these studies. Masini et al did measure drug concentrations of two cytostatic drugs. However, they concluded that the accuracy of the concentration

of active ingredients could not be calculated because bags are generally overfilled by pharmaceutical companies with different amount of diluents, making it impossible to determine the drug's final concentration.[9] When using drug concentrations to compare accuracy, overfilling of the bags is an important factor to take into account in the study design.

As yet, no data have been published on the accuracy of compounding robots wherein the actual concentration of the end product is measured. This means that it is unknown whether the robotic method of preparation differs from the manual method in terms of the actual amount of active substance that is delivered to the patient.

We compared the accuracy and precision of the automated and manual prepared cytostatic dose by means of measuring drug volumes and drug concentrations.

METHODS

Setting

This study was conducted from March 4 to March 15, 2019 in the centralized cytotoxic drugs preparation unit of the OLVG hospital in Amsterdam, The Netherlands. The OLVG oncology department comprises 48 inpatient beds and 17 outpatient seats. Cytostatic products such as infusion bags, elastomeric pumps, and ready-to-administer syringes are prepared in a biological safety cabinet (BSC) class A and in the robotic system APOTECAchemo (Loccioni, Italy), placed in the same Grade C cleanroom with negative air pressure (-5 Pa). The annual workload amounts to 13.000 cytostatic preparations.

The robotic system is designed for patient individual ready-to-use parenteral doses and consists of a loading area and a compounding area. The pharmacy technician loads the starting materials (drug vials, intravenous fluid bags, syringes, elastomeric pumps and needles) and unloads the finished products, which are both temporarily stored in a rotating warehouse. All drug vials are identified by photo recognition, height and weight. Final products wherein the amount of active substance differs by more than 10% from the prescribed amount, will be automatically rejected. In the compounding area, the robotic arm prepares the individual doses using gravimetric quality control. The weighing system of the robot is calibrated internally and externally on a daily basis. In addition to that, the manufacturer verifies the weighing system calibration half-yearly.

Aseptic compounding

Methotrexate (MTX) and cyclophosphamide (CP), two common cytostatic drugs, were the drugs of choice to compare the dose accuracy between the robot preparations and manual compounding. MTX 50mg was selected because it is the smallest volume (2ml) of this drug that is administered intravenously. CP was selected because the vials contain powder that is difficult to dissolve during preparation.

Table 1. Overview of all preparations.

Day	No of the preparations	No of preparations each day	Final container	Drug vial used	Drug dose
1 - 5	1 - 40	4 robot and 4 manual	Normal Saline bag 100ml	cyclophosphamide 1000mg powder or cyclophosphamide 2000mg powder	1200 mg
6 - 10	41 - 80	4 robot and 4 manual	Normal Saline bag 50ml	methotrexate 25mg/ml 20ml	50 mg

During ten days 80 solutions were prepared; 40 robot preparations and 40 manual preparations (table 1). With both preparation methods, 20 methotrexate and 20 cyclophosphamide bags were compounded. Normal Saline 50ml (NaCl 9mg/ml new viaflo; lot number 18K24G63) and Normal Saline 100ml (NaCl 9mg/ml new viaflo; lot number 19A04G61) infusion bags were used for the MTX and CP preparations, respectively. MTX 500mg=20ml vials (Pharmachemie BV, batch number 18H17OD) were used. CP 2g and 1g vials of Sandoz were used with batch numbers JE8143 and JE7853, respectively. With robotic preparation glass vials of water for injection (aqua ad injectabilia 100ML; B.Braun medical BV; lot number 194018072) and for manual preparation plastic vials of water for injection (100ml ecoflac; Baxter BV; lot number 19023401) were used. All 80 bags were emptied and manually refilled with a known volume to eliminate possible variability due to overfilling of the bags by the manufacturer. The bags were weighed before and after refilling to exactly know the weight and volume of Normal Saline in the bags. The bags were weighed again after adding of the drug. The added amount of drug was calculated accurately by subtracting the weight of the Normal Saline filled bag from the total weight of the bag. The volumes were calculated by dividing the added drug weight by the drug density. The density of the MTX (1.014 g/ml) and CP solution after reconstitution with water for injection (1.006 g/ml) was obtained from the manufacturers. The finished preparations were stored with a light-shielding overbag in the refrigerator (2-8 ^{o}C).

The manual preparations were executed by three different pharmacy technicians. We simulated regular working conditions by performing the preparations on Monday till Friday.

Sample analysis

MTX and CP concentrations were determined with validated ultra high performance liquid chromatography (UHPLC) methods using CORTECS®C18 2.7µm 3.0x150mm columns from Waters (lot number 186007373). Mobile phase used was a buffered solution of acetonitrile. For CP analysis, internal standard methyl-4-hydroxybenzoate in methanol is used in a concentration of 0.1 mg/ml. For MTX no internal standard was available.

All forty MTX preparations (day 1-5) were analysed in the same run on the last preparation day (day 5). Also all CP preparations were analysed in the same run on the last preparation day. The calibration curves for MTX were linear from 0.69 mg/ml up to 2.08 mg/ml, giving a correlation coefficient r2 = 0.99986. The calibration curves for CP were linear from 5.67 mg/ml up to 8.49 mg/ml, giving a correlation coefficient r2 = 0.99874.

We calculated the amount of cytostatic drug in the bags by multiplying the drug concentration with the number of millilitres. According to the Dutch Medicines Act, the determined amount of the active substance should differ by less than 10% from the prescribed amount.[11]

Data analysis

The statistical package SPSS (Statistical Package for the Social Sciences, SPSS Inc., Chicago, Illinois, USA) was used to analyse the data. Independent samples T-test was performed to investigate the difference in dose accuracy of two different preparation methods. Levene's test for equality of variances was performed to investigate the precision of the two different preparation methods. A p-value < 0.05 was considered statistically significant.

RStudio 1.1.383 was used to create fig. 1-3.

RESULTS

By each compounding procedure, 20 MTX (50 mg in 50 ml) and 20 CP (1200 mg in 100 ml) were compounded. This resulted in a total of 80 preparations, 40 by manual production and 40 by the robot, respectively.

Methotrexate UHPLC analysis

Dose accuracy (mean absolute dose error) and precision (standard error) of robotic preparation of MTX were -0.85 mg (-1.70%) and 0.19 mg (Fig. 1). In the manual preparation, these values were 0.48 mg (0.96%) and 0.84 mg. Dose accuracy did not differ significantly between both preparation methods (p =0.132). The standard error of the robotic preparation for MTX was significantly smaller than that of manual preparation (p < 0.001).

Methotrexate gravimetric analysis

Dose accuracy and precision of robotic preparation of MTX were 0.25 mg (0.50%) and 0.44 mg (Fig. 1). In the manual preparation, these values were -0.98 mg (-1.96%) and 0.33 mg. The accuracy of the robotic preparation for MTX was significantly better than that of manual preparation (p = 0.032). The standard error did not significantly differ between both preparation methods (p = 0.597).

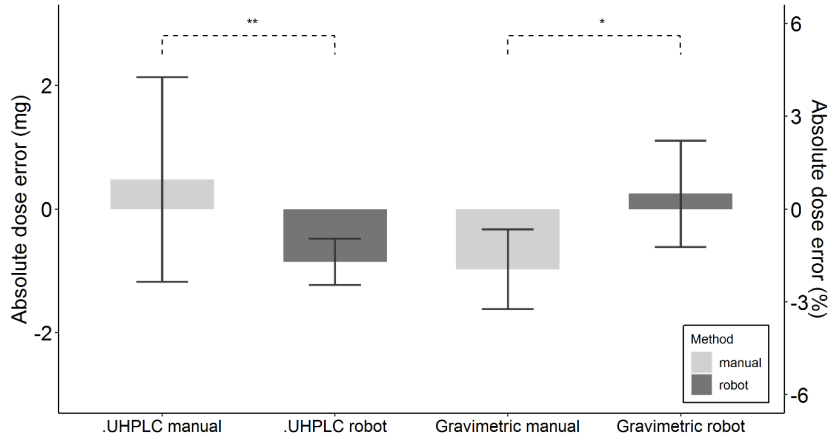

Fig. 1. Dose accuracy (mean absolute dose error) and precision (standard error) of robotic versus manual preparation of methotrexate (MTX). From left to right, the first two plots show ultra high performance liquid chromatography (UHPLC) analysis results with the dose accuracy of MTX after manual (plot 1) and robotic (plot 2) compounding. Error bar indicates 95% confidence interval of standard error. *The accuracy of the robotic preparation of MTX was significantly better than that of manual preparation (p = 0.032). **The standard error of the robotic preparation of MTX was significantly smaller than that of manual preparation (p < 0.001). The third and fourth plot respectively show the dose accuracy of manual (plot 3) and robotic (plot 4) compounding, using the weight of added amount of active drug.

Cyclophosphamide UHPLC analysis

There were no significant differences in dose accuracy (p = 0.429) and precision (standard error, p = 0.786) between robotic preparation and manual preparation of CP. Dose accuracy and precision of robotic preparation n of CP was -73.61 mg (-6.1%) and 9.83 mg (Fig. 2). In the manual preparation, these values were -62.13 mg (-5.2%) and 10.45 mg.

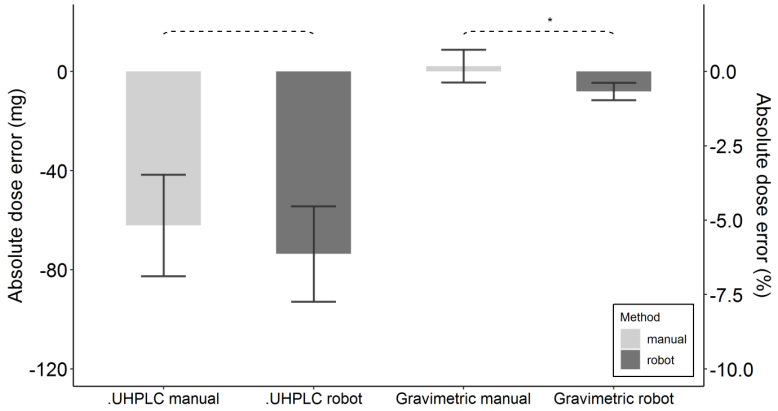

Fig. 2. Dose accuracy (mean absolute dose error) and precision (standard error) of robotic versus manual preparation of cyclophosphamide (CP). From left to right, the first two plots show ultra high performance liquid chromatography (UHPLC) analysis results with the dose accuracy of CP after manual (plot 1) and robotic (plot 2) compounding. The third and fourth plot respectively show the dose accuracy of manual (plot 3) and robotic (plot 4) compounding, using the weight of added amount of active drug. Error bar indicates 95% confidence interval of standard error. * The accuracy of the manual preparation for CP was significantly better than that of robotic preparation.

In Fig. 3, CP results are shown for each preparation day. During the manual preparation week, a linear trend is visual, indicating that there is most likely some loss of CP during storage. After robotic preparation, such a trend is less clear.

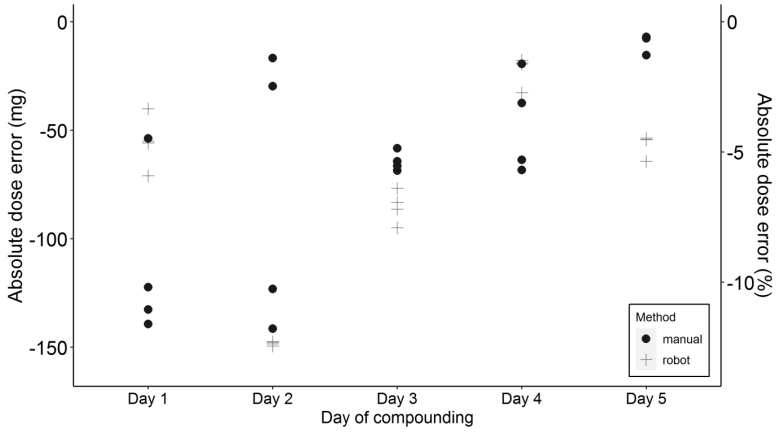

Fig. 3. UHPLC analysis of all 40 cyclophosphamide samples to illustrate the dose error over the week of compounding. Each compoundig day, four manual and four robotic preparations of cyclophosphamide were compounded. UHPLC analysis of all samples was on day 5.

Cyclophosphamide gravimetric analysis

Dose accuracy and precision of robotic preparation of CP was -8.09 mg (-0.67%) and 1.80 mg (Fig. 2). In the manual preparation, these values were 2.16 mg (0.18%; p = 0.011) and 3.36 mg (p = 0.421). The accuracy of the manual preparation for CP was significantly better than that of robotic preparation.

DISCUSSION

This study is the first to compare accuracy and precision of automated preparations with manual preparations by measuring volumes and drug concentrations. Thus far, no actual drug concentrations in the end product were measured, which means that not the entire process of automated preparation was compared to manual preparation. Hence, it was unknown whether the robotic method of preparation differs from the manual method in terms of the actual amount of active substance that is delivered to the patient.

We conclude that both automated and manual compounding produce accurate cytostatic products in which the mean percentage of active substance differs by less than 10% from the prescribed amount. Both preparation methods are compliant with the Dutch Medicines Act and the European Pharmacopoeia.[11,12]

Our results are in agreement with those of Masini et al who also concluded that both automated and manual production led to accurate and precise dosages.[9] In our study, robotic preparation of MTX was more precise (UHPLC analysis) and more accurate (gravimetric analysis). Iwamoto et al. concluded that robotic preparation was more accurate and precise than manual preparation.[7] Amodeo et al. concluded that robotic preparation of cytostatics was more precise than manual preparation.[8]

None of the 80 samples of our gravimetric analysis exceeded the dose limit of 10%.[11,12] This is in line with previous studies doing gravimetric analysis during automated production, showing low percentages (1.1% in 1509 samples [3] and 0.07% in 7384 samples [2]) of all preparations exceeded the limit of 10%.[12] However, our results of gravimetric analysis during manual production are not in line with Poppe et al. in which 12.6% of all 1156 preparations exceeded the limit of 10%.[5] A possible cause of this finding could be that in our study the pharmacy technicians were aware of the fact their prepared samples were analysed afterwards. This analysis does not happen during regular working conditions with manual compounding and can cause bias.

Of all 80 UHPLC samples, 13 exceeded the dose limit of 10%, of which four were automated preparations (all CP) and nine were manual preparations. In addition, nine out of these 13 were CP preparations. This is in contrast to results found after gravimetric analysis in previous studies with automated production, which showed low percentages of preparations exceeded the limit of 10%.[2,3] Subsequently, comparing the UHPLC analysis and the gravimetric analysis of CP preparations gave different results. In gravimetric analysis the doses of the CP preparations were within 1% of the declared content, while the same CP bags show a much greater deviation after UHPLC analysis (respectively 6.1% and 5.2%). Two possible causes of these findings are the stability of CP and incomplete dissolution of CP during preparation.

Poor stability of dissolved CP possibly contributed to the high deviation of some dosages, as shown in Fig 3. We analysed all samples in a single run after 1-4 days after preparation, assuming a 7-day shelf life of CP when stored at 4^0C protected from light.[13] All preparations were analysed on day 5. The UHPLC method does not measure degraded CP. A larger time span between preparation and analysis allowed for more degradation and resulted in a greater deviation from the declared content. However, not all samples fit well with this hypothesis, with automated preparations on Mondays and Fridays not precisely matching this trend.

Secondly, incomplete dissolution of CP possibly contributed to the lower dosages found after UHPLC analysis of CP samples. This possible outcome underlines the importance of concentration determination in the end product. However, both preparation methods incorporated a visual check by the technician to ensure complete dissolution. If CP dissolution was incomplete, then Fig. 3 shows that automated production allows for more consistent dissolution of CP. This can be explained by the programmed mixing speed and dissolution times during automated production, while during manual production these factors depend on the technician.

When comparing the accuracy of automated and manual preparations, both methods of preparation perform well. In the UHPLC analysis no differences in accuracy were found. Gravimetric analysis showed more accurate MTX doses for automated preparations (0.50% vs 0.96%), and more accurate CP doses for manual preparations (0.67% vs 0.18%). The observed differences were small and are not clinically relevant.

Although both automated and manual preparations led to precise dosages, two findings suggest an advantage of automated production. First, MTX preparations showed in the UHPLC analysis more precise dosages for automated preparation. However, no differences were found in the precision in the gravimetric MTX analysis. Secondly, the UHPLC

analysis showed that the CP doses revealed interday variability and were much closer to each other after automated production, especially on Monday, Tuesday and Thursday. Although there is no strong evidence that automatic chemotherapy production results in less spread in dosages, we tried to provide arguments that support this hypothesis. The positive findings in favour of automated preparation can be explained by the fact that the automated movement of the robot arm is pre-programmed, and it is not influenced by the eyes of the technician or the printed scale on the syringe. The inner diameter of the syringe and the accuracy of the scale of the syringe cause variances during manual preparation.[14] In addition, for the MTX samples, the small volume of 2 ml MTX could result in a larger variation in the amount of MTX.

In our study, MTX and CP were the drugs of choice to compare the dose accuracy between the robot preparations and manual compounding. Different variables can be taken into account when selecting the drugs. Obviously, an assay should be available to determine drug concentrations. Also it is preferable to work with common cytostatic drugs so the results are important for daily practice. All drugs have different physicochemical properties that can affect the accuracy and precision of the preparation process. Poppe et al have shown that manipulation of small volumes and dissolution of powders gave more variation in accuracy of the dose.[5] Therefore, MTX 50mg was selected because it is the smallest volume (2ml) of this drug that is administered intravenously. And CP was selected because the vials contain powder that is difficult to dissolve during preparation. In this way, also the dissolving step is included in the comparison of both preparation methods.

Our present study is the first study that compares accuracy and precision of robot preparations with manual preparations by measuring drug concentrations and volumes. Four earlier trials are available, where accuracy and precision is compared with only gravimetric results.[7-10] In our setting, both preparation methods and both analysing methods, measuring drug concentrations and measuring drug volumes, provide accurate and precise cytostatic dosages.

A strong point of our study is that we performed this qualification on multiple days with rotating staff, thus simulating an actual working week. Furthermore, we simulated different types of cytostatic drugs and preparations, which included a powder (CP) and a small volume drug (MTX). CP preparation analysis gives us a comparison of both preparation methods with a powder that is difficult to dissolve. In addition to measuring the number of millilitres of drug volume, we also compared the drug dissolution step by measuring the drug concentration of CP. By preparing MTX 50 mg, we were able to study

the performance of a robot versus pharmacy technicians when adding a small volume of concentrate to a diluent.

Clearly, there are also limitations to the present study. Firstly, our study was performed in a single centre. Hence, extrapolating our results to pharmacies with different pharmacy technicians and different cytostatic robots can cause variation in results. Secondly, all drugs were analysed at the same moment, while preparation took place at different days of the same week. This could have led to more degradation in preparations at the beginning of the week. This has most likely been the case with CP, resulting in more degradation over storage time. These results are also interesting because we now know the actual CP dose if we prepare CP several days before administration. In practice, we prepare one day in advance. Four days after preparation, the mean dose remains within the legal 10% deviation. Thirdly, in our study the pharmacy technicians were aware of the fact their prepared samples were analysed afterwards. This could cause bias and lead to different results.

Future studies are needed to repeat our investigation in settings where other cytostatic robotic systems are present, different drugs are used and different technicians are trained. To select drugs for analysis, we suggest to use common cytostatic drugs with different physicochemical properties, such as foaming solutions like cabazitaxel or viscous solutions like paclitaxel. Also our investigation can be repeated with different final vehicles including syringes as well as elastomeric pumps for home infusion. For the design of future studies, we suggest to also determine the concentration of the reconstituted solution, so you also know the exact initial concentration. In this way, you can analyse the completeness of dissolution of powdered drugs and you can correct for a possible difference between the actual drug concentration in a vial and the concentration stated by the manufacturer.

In conclusion, both robotic compounding of cytostatic drugs with APOTECAchemo as well as manual compounding results in accurate and precise dosages.

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