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Qualification and Performance Evaluation of an Automated System for Compounding Injectable Cytotoxic Drugs

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Abstract

Background: Use of automated systems for the production of chemotherapy will increase in answer to hospitals' needs to rationalise production. The aim of the study was to evaluate the performance of a PharmaHelp® automated system for compounding chemotherapy.

Methods: Viable and non viable particles in air and liquid were measured by particle counter. Surface chemical contamination was simulated with a quinine solution. Microbiological contamination and aseptic processes were studied using media-fill tests. Dose accuracy was evaluated using a gravimetric method, in simulation studies and with real products in daily practice. Productivity was calculated by batch of ten IV-bags.

Results: No particles or microbiological contamination were detected. Filling was accurate for all the volumes of non-viscous solution studied (97–103 %). Minimum volumes which could be prepared accurately were 2 mL and 5 mL for the non-viscous and viscous solutions, respectively. For 2–5 mL volumes, the robot was less accurate than average, and 0–2% of bags were rejected (deviation > 10 %). Average fill deviations were from 0–3 % for 2–5 mL volumes and < 1 % for volumes above 5 mL. Average production time for ten bags was 61 ± 11 min.

Conclusions: The automated system was able to produce chemotherapy effectively, delivering appropriate quality with productivity comparable to manual preparations. These results confirmed that such automated systems have the potential to guarantee optimal safety for patients and technicians.

Keywords: cytotoxic drugs, compounding, robot, performance, qualification

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Introduction

In 2002, our hospital centralised injectable cytotoxic drug compounding at its pharmacy; this unit now manufactures all cancer therapies known to be carcinogenic, mutagenic and toxic to reproduction. Since 2006, demand for chemotherapies has increased gradually but continuously. The pharmacy prepared 12,554 chemotherapy doses in 2006, and 15,707 in 2017—a 27 % increase. With budget constraints preventing the hiring of additional pharmacy technicians, this increase forced processes to be rethought and innovative streamlining solutions to be found. One strategic choice was opting for automated systems and switching some production to standard doses (dose-banding). The reasons were manifold: increase efficiency (anticipate and smooth-out activity across the day) [1], ensure preparation quality (accuracy, robustness, reproducibility by reducing human errors) [2, 3], decrease staff exposure to toxic chemotherapies [3, 4], improve working conditions (reduce fatigue and musculoskeletal disorders) and limit human resources expenditure.

The advent of robotics in chemotherapy is not recent (first published in 1989) [5] but only a few hospitals have actually implemented this technology. Good manufacturing practices require a complete qualification validation of all production equipment, but no specific guidelines exist for automated compounders and literature on qualification and validation methodologies is scarce [1, 6]. This article's purpose is to present the advantages and disadvantages of using automated compounders for the

production of injectable cytotoxic drugs through an evaluation of a robot's performance.

Materials and methods

Equipment

Description of equipment

The PharmaHelp® oncology compounder (Fresenius Kabi, Bad Homburg, Germany) is a recently-developed device designed to produce bags of antineoplastic drugs. It consists of four elements: the server; the pre-processing station with a balance coupled to an RFID scanner and a camera; the production station itself (syringe carousel, pinches and the robot head, coupled to an RFID scanner); and the post-processing station, with a balance coupled to an RFID scanner (see Figure 1).

As per current recognised recommendations (US Pharmacopoeia P 800, Swiss Pharmacopeia and PIC/S guidelines), the automated system was installed in a Grade C negative air-pressure cleanroom (ISO 7). The pre-processing and production stations were installed in two Grade A Class III biological safety cabinets (BSC) (ISO 5).

The roles of each element were as follows:

- the server contained all data and the PharmaHelp® software for controlling production steps and recording the audit trail;
- the pre-processing station assigned each drug and each bag to an support with an RFID chip; the software recorded the weight of each item (see Figure 1: bottom photo, first from left);
- the production station recognised the positions of the different production materials thanks to the RFID tags and produced the cytotoxic drugs bags (see Figure 1: bottom photo, second from left);
- the post-processing station identified different IV bags thanks to their RFID tags and verified the final weight of the products (see Figure 1: bottom photo, third from left).

The PharmaHelp® system was able to produce a maximum of ten IV bags in a single run, with a maximum of six different drugs. This was interfaced with our

Figure 1: PharmaHelp® automated compounder: pre-process, production and post-process zone (from the left to the right on the photo).

electronic chemotherapy management system, including electronic prescribing, and safety was ensured in four ways: a visual recognition system (camera) and an RFID tag scanner to ensure that the correct drug was in the correct container, a gravimetric check for drug dose accuracy and an electronic record of all production steps.

The process

The PharmaHelp® compounder's manufacturing process consisted of six steps: prescription, material collection, pre-processing, production, post-processing and release of the final product.

a) Prescription step: after determining the patient's treatment protocol, the order was electronically prescribed by medical staff, using software developed in-house (CytoDemande), and then sent to the pharmacy's in-house software (CytoPrepare). Chemotherapies suitable for preparation by PharmaHelp® were selected by pharmacy technicians and sent to the PharmaHelp® server via an interface developed jointly by the manufacturer and our IT department.
b) Material collection step: the PharmaHelp® server printed a list of all the materials to collect for manufacturing the run of chemotherapies. The technician prepared all the materials and documented each item's batch number using the PharmaHelp® software. Validation of all the information on the collection list was sent to the pre-processing station along with the order.
c) Pre-processing step: the technician prepared the medical devices (supports for vials and bags) and disposables (PharmaVent®, PharmaNeedle®, syringes, caps) needed for preparation by the robot in the pre-processing element's BSC. If necessary, the technician reconstituted the drug vials and inserted the IV lines onto the diluent IV bags. Supports were fixed on each diluent bag, trash bag and vial. Each component was then identified by the camera and weighed by the balance at the same time. The correct identification was then assigned to each component's RFID tag.
d) Production step: the technician inserted a venting needle (PharmaVent®) into the vials and added an admixing needle to the syringe. The syringes were placed on the carousel, and the vials and bags were put in the robot according to their support. The technician verified that the installation was correct and launched the automated production process in the production element's BSC. After automatic recognition of vials and IV bags according to their RFID tags, the robot withdrew the necessary volumes of drugs from the appropriate vials and injected those volumes into the corresponding final IV bags.
e) Post-processing step: each IV bag produced was identified by the RFID tag on its support. Its contents were verified using a gravimetric method, and any deviation between the measured and theoretical weights was calculated.
f) Release step: depending on the parameters selected (up to a 10 % discrepancy according to the hospital's good manufacturing practices), the PharmaHelp® proposed either release or rejection of chemotherapy IV bags. Any rejections had to be manually confirmed and documented. The server recorded all the information about every step in the chemotherapy compounding process and transferred it to our in-house CytoTrace software for traceability purposes.

Materials

Specific PharmaHelp® materials

Sterile disposables associated with the oncological compounder:

- Luer-Lock 50 mL syringes (Codan, Rodby, Denmark);
- PharmaNeedle® (Fresenius Kabi Deutschland GmbH, BadHomburg, Germany) large gauge needles (17 G) with a sidelight; these reduced chemical contamination (by a factor of ten, manufacturer's data), facilitated the withdraw of liquid at the bottom of vials and were adapted to multiple samples;
- PharmaVent® (Fresenius Kabi Deutschland GmbH, BadHomburg, Germany) air intakes, equipped with a 1.2 µm removable polypropylene filter and bent at 90° to keep the vial septum available for a filling needle;
- PharmaHelpBag® (Fresenius Kabi Deutschland GmbH, BadHomburg, Germany) rubbish bags which allowed the elimination of part of the diluent when a bag had to be produced with a fixed volume.

Medical device associated with the oncological compounder:

- Supports equipped with an RFID tag (Fresenius Kabi Deutschland GmbH, BadHomburg, Germany) for the above vials and bags.

Materials for qualification and validation

Chemical contamination

Vials of quinine dihydrochloride (batch 039556071B, Courtin-Warner Ltd, Lewes, UK) 40 mg/mL.

Accuracy

Materials used were: Luer-Lock 1, 3, 5, 10, 20 and 50 mL syringes (BD, Franklin Lakes, USA); 18 G (1.2_40 mm) and 22 G (0.7_30 mm) needles (Terumo, Leuven Belgium); 100 mL vials of NaCl or water for injection (Fresenius-Kabi, Bad-Homburg, Germany); 50, 100, 250, 500 mL NaCl and glucose bags (Sintetica SA, Mendrisio, Switzerland); two precision Sartorius Cubis MSE model MSE2203S-1CE-DR balances (d = 0.001 g, e = 0.01 g), max 2200 g, min 0.1 g (serial numbers 34,005,447 and 34,005,446), and one precision Mettler Toledo ME2002 balance (d = 0.01 g, e = 0.1 g), max 2200 g, min 14.0 g (serial number B514793273).

Methods

The method was designed so as to provide a standard qualification master plan, transferable to any oncological compounder.

The key to qualification and validation exercises is to provide a high level of documentary evidence that both equipment and processes conform to quality and safety standards.

Qualification of pharmaceutical [7–9] equipment involves the following:

- Installation qualification (IQ) verifies that equipment has been properly installed, in accordance with manufacturers' recommendations and in an environment suitable for its intended purpose.
- Operational qualification (OQ) is done to provide a high degree of assurance that the equipment functions as intended and to determine whether the entire system operates as an integrated whole.
- Process performance qualification (PQ) verifies that the system is repeatable and consistently produces a quality product.
- Process validation uses an experimental approach to verify that the equipment's performance, in its normal operating environment, is consistently exactly as specified in the user requirements specification.

The present article focuses on elements of particular interest to hospital pharmacists: chemical accuracy, surface contamination, microbiological validation of the process and productivity.

Process qualification and validation

Process validation tests were performed in real operational conditions, following the manufacturing process, from electronic prescribing to release of the preparation.

Chemical accuracy

Any deviations from target measured at greater than ± 3 %, ± 5 % and ± 10 % were reported and discussed.

These limit values were inspired by the following sources:

- ± 3 % is the accuracy recommended by the International Electrotechnical Commission for highly accurate infusion pumps—although our robot is not considered an infusion pump, it nonetheless has very similar characteristics [10];
- ± 5 % is, in clinical practice, the usual limit of dose variation recommended for high-risk drugs [11];
- ± 10 % is the maximum variation in dose permitted in production by the European Pharmacopoeia [12] and Swiss Good Manufacturing Practices.
- The robot was considered by our services as a high precision pump. In this sense, it must meet the specifications of medical devices. Higher tolerance was accepted for small volumes (< 5 ml) and viscous products. Based on these considerations and regulatory data, the following precision acceptance criteria (user specifications) were defined:for non-viscous finished products with a volume less than or equal to 5 mL, a dose deviation of ± 5 % (95 % CI) from the prescribed dose is tolerated,
- for non-viscous finished products with a volume greater than 5 mL, a dose deviation of ± 3 % (95 % CI) from the prescribed dose is tolerated,
- for viscous finished products, a dose deviation of ± 5 % (95 % CI) from the prescribed dose is tolerated.

Accuracy was defined as the value of the relative error, that is ((measured dose minus prescribed dose)/prescribed dose). The measured dose was calculated by the weight difference between the IV bag before and after chemotherapy or NaCl 0.9 % injection; it was based on specific gravity. If those weights are known, therefore, it is possible to accurately ensure the amount and type of anticancer drug injected into the bag in preparation.

Accuracy in operational qualification (OQ)
These steps involved only the robot processes without connection to the prescription software, CytoDemande. Six batches of ten test-preparations with different admixing volumes (2–250 mL water for injection in NaCl 0.9 % bags) were programmed directly into the robot. These batches were prepared for three of our manufacturing conditions: withdrawal of diluents (cytotoxic preparation with a fixed final volume), injection volume in production in series (fixed dose, simulation of dose-banding) and production by range (escalating dose, simulation of individual dose). Balances had been calibrated and each weight was controlled using an independent Mettler Toledo balance.

Accuracy in the performance qualification (PQ)
These steps involved all the processes of chemotherapy production, integrated from prescription to delivery of the final product. Two types of solutions were tested: non-viscous and viscous solutions. For the non-viscous solution, three batches of ten test-preparations were prepared over three different days, under routine working conditions, with different admixing volumes (2–250 mL water for injection in NaCl 0.9 % bags) for two of our manufacturing conditions: injection volume in production in series (fixed dose, simulation of dose-banding) and production by range (escalating dose, simulation of individual dose). Balances had been calibrated and each weight was controlled using an independent Mettler Toledo balance. For the viscous solution, twenty vials of paclitaxel-like solution were prepared. Each vial contained 50 mL of a solution composed of 57 % w/w macrogol ricinoleate (Cremophor® EL kindly donated by Impag AG Switzerland) 43 % w/w ethanol [13, 14]. Viscosity was measured using a digital viscometer (Rheostress 1 Haake, Germany, titanium cone plane geometry, D = 60 mm, 1°) and was close to 27 MPa, as described by the manufacturer of paclitaxel (Taxol®). Three of the robot's parameters were tested for the withdrawal: the normal, oily and syrupy settings (velocity of the piston movement when withdrawing and adding liquid volume).

Preparation for patient care
During a one year reporting period, the number of production runs processed and bags produced, as well as results for accuracy, were assessed by analysing the data collected by the device's software.

Chemical contamination

Surface contamination
– Quinine test

The quinine test aimed to get a risk assessment of working environment contamination after production. This was carried out in two steps: a technician reconstituted 200 mg quinine vials with 5 mL water for injection and used them as raw material for production by the automated PharmaHelp® system. At the end of production, quinine spots were revealed by exposure to UV light and counted. Their sizes were measured on the floor of the processing BSC, IV bags, syringes and supports, as described by Sadeghipour et al [15]. This experiment was repeated with three different batches, on three different days, with three different technicians.

Microbiological validation

– Media fills

Three media fills were carried out on each of three consecutive working days using the PharmaHelp®. The media fill program for any aseptic manufacturing process must represent a worst case situation and include all manipulation and interventions likely to be represented during a shift. Process intervention must consider routine (typical) and non-routine (atypical) event. Routine intervention was represented by hand alarm detection and non-routine intervention by the stop of the ventilation that could occur in case of equipment failure. Worst-case conditions were applied in two runs out of three:

– during filling in the second run (worst-case A), the technician stopped the robot by triggering the hand alarm detector;
– during filling in the third run (worst-case B), the technician stopped the robot and ventilation for 1 min.

The media-fill test was done in two parts. First, a trained technician transferred tryptone soya medium from flasks to sterile vials in an aseptic environment, following good manufacturing practices. This was done manually in the pre-processing BSC. Next, the PharmaHelp® robot, in the processing BSC, injected 41.5 mL of Casein Soya digest medium (Ph Eur) into ten IV bags of 50 mL 0.9 %. Then, an air volume of 10 mL was withdrawn from the grade A environment of the BSC and manually added into each IV bag.

According to European Pharmacopoeia specifications (section 2.6.1), bags filled with media and vials were then incubated for 7 days at room temperature and then 7 days at 32.5 °C. Possible results were *contaminated* or *uncontaminated*.

Productivity

The total time needed for the pre-processing, processing and post-processing steps was assessed. Three production runs were processed on three different days by different staff members. Experimental conditions were defined from the most frequently found real production situations. The tests focused on:

- volume injected: 3–50 mL of injected volume of chemotherapy;
- different molecules used: 1 to 5 different molecules per run;
- number of vials: 3 to 7 vials per run;
- final number of preparations: ten IV bags.

Three steps were monitored:

- pre-processing: disinfection and transfer of materials into the input aseptic production transfer airlock, gloving, transfer of materials to the workbench, handling of materials on the workbench, bag filling and connecting the IV tubing;
- processing: automated withdrawal and injection of medical products into the IV bag;
- post-processing: gravimetric-based checking, labelling and final delivery.

Productivity measurements did not include any withdrawals of diluent solution. Results were compared to the average times for manual preparations, carried out using a gravimetric system (CATO®, BD) in a class III BSC. Manufacturing time comparisons measured one automated ten-preparation run with the robot versus ten manual preparations carried out in July 2016.

Statistical analysis

Descriptive statistics (mean, median, standard deviation (SD) and 95 % confidence intervals (95 % CI)) and simple analyses ($\chi 2$ tests) were conducted. A p-value ≤ 0.05 was considered statistically significant.

Results

Qualification and validation of the automated PharmaHelp® system took place from May 2015 to July 2016.

Qualification/validation of the process

Chemical accuracy

Accuracy (OQ)

For both the individual doses (N = 60) (see Figure 2) and series (dose banding, N = 90) (see Figure 3), the injected volumes of 5–250 ml were highly accurate (trueness and precision), with deviations and SDs ≤ 1 %. Volumes from 2–5 mL were less accurate, with deviations between 1 % and 3.4 %, and SDs between 1.3 % and 3.5 %. An underfill trend was observed for the injected volume.

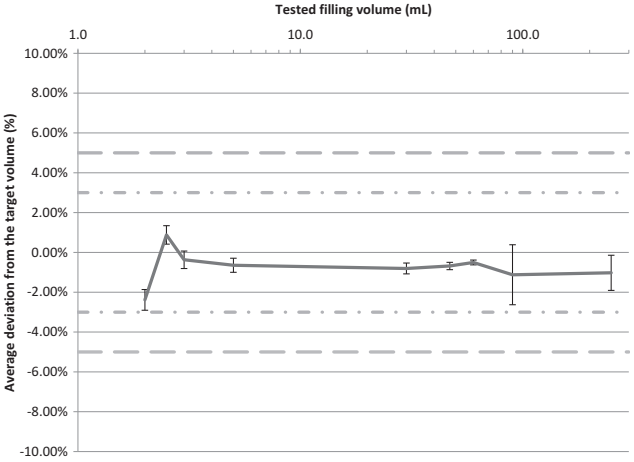

Figure 2: Filling accuracy (relative error ± 95 % CI) of the PharmaHelp® automated compounder, for individual doses carried out for operational qualification (6 batches of 10 bags, N = 60 IV bags).

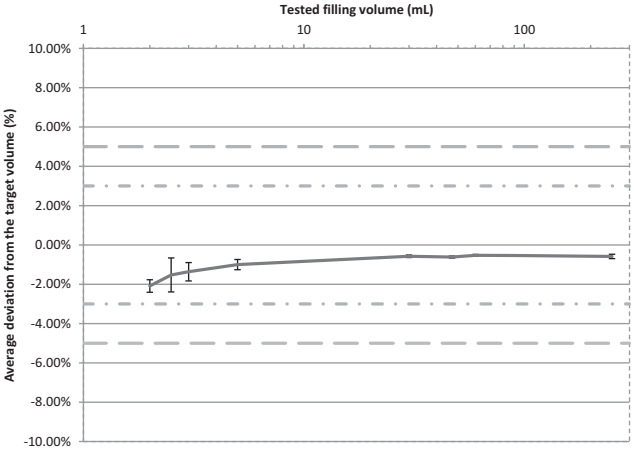

Figure 3: Filling accuracy (relative error ± 95 % CI) of the PharmaHelp® automated compounder, for a series (standard doses or dose banding) carried out for operational qualification (9 batches of 10 bags by tested volume, N = 90 IV bags).

For withdrawn volumes (N = 60) (see Figures 4, 5), volumes from 5–250 mL were also highly accurate (trueness and precision); deviations and SDs were ≤ 1%. Volumes from 2–5 mL had a lower trueness with deviations between 1% and 3.9%, and an overfill trend was observed.

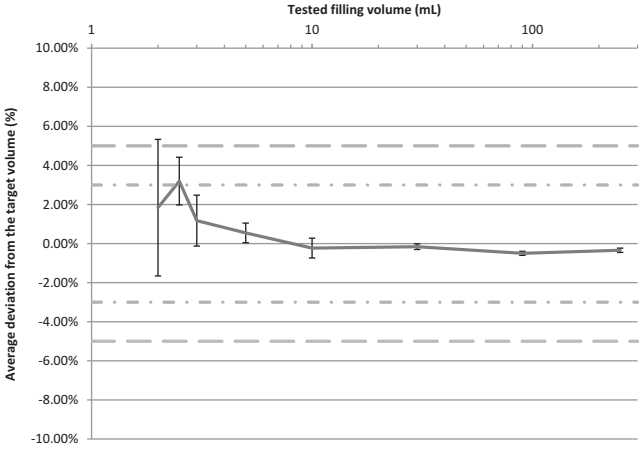

Figure 4: Filling accuracy (relative error ± 95% CI) of the PharmaHelp® automated compounder, for withdrawn volume of individual doses carried out for operational qualification (6 batches of 10 bags, N = 60 IV bags).

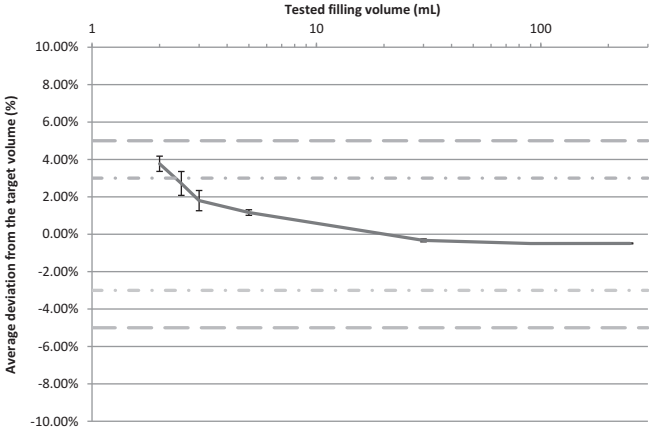

Figure 5: Filling accuracy (relative error ± 95% CI) of the PharmaHelp® automated compounder, for a series of withdrawn volumes (standard doses or dose banding), carried out for operational qualification (6 batches of 10 bags, N = 60 IV bags).

The 2 mL withdrawal volume for individual doses was the only one outside of specification (relative error ± 95% CI > 5%) (see Figures 2, 3, 4 and 5). The automated system thus met our specifications for other volumes from 2–250 mL, even though some rejections (0%–3%) were detected for the first bag in runs with fixed dose (series) involving small volumes (2–5 mL).

Accuracy (PQ)

Non-viscous solution

For the individual doses (N = 60) (see Figure 6) and series (dose banding, N = 90) (see Figure 7), the results were similar to those for the operational qualification. Filling was true for all the studied volumes (97%–103%).

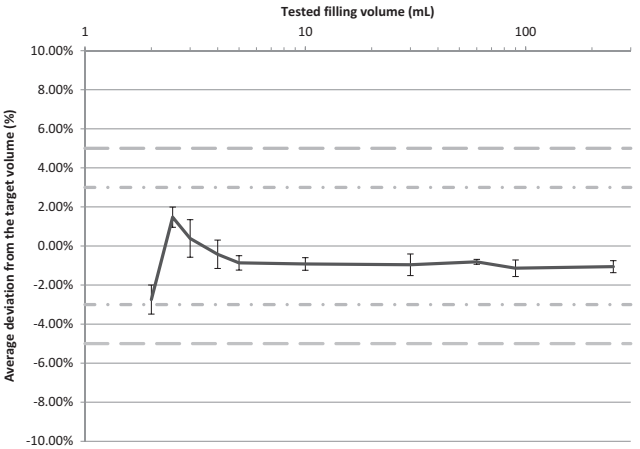

Figure 6: Filling accuracy (relative error ± 95% CI) of the PharmaHelp® automated compounder, for individual doses carried out for performance qualification (9 batches of 10 IV bags, N = 90 IV bags).

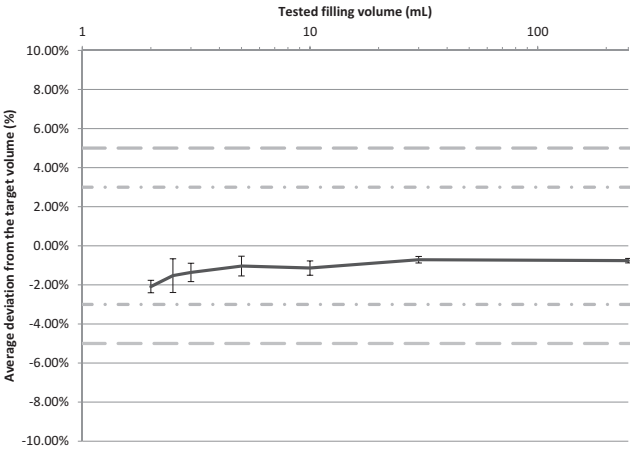

Figure 7: Filling accuracy (relative error ± 95% CI) of the PharmaHelp® automated compounder, for a series (standard doses or dose banding) carried out for performance qualification (9 batches of 10 IV bags by tested volume, N = 90 IV bags).

The automated system met our specifications for volumes from 2–250 mL. The 2 mL volume for individual doses was the only one to be above the ± 3% of deviation (but under ± 5%). For other volumes from

3–250 mL, the relative errors ± 95 % CI were under ± 3 % (see Figures 6 and 7).

Viscous solution

For the individual doses of viscous solution (N = 36) (see Figure 8) and series (dose banding, N = 45) (see Figure 9), injected volumes from 2–25 mL were less true (96%–102 %) and accurate than for the non-viscous solution.

For series, both deviations and SDs were ≤ 1% for volumes from 5–25 ml. Volumes from 2–5 mL were less accurate, with deviations between 3.9 % and 5.8 % and SDs between 2.1 and 10.

The relative error ± 95 % CI was above ± 5 % for volumes less than 5 mL. The relative error decreased to below the limit of ± 5 % for volumes from 5–25 mL. By extrapolation, the automated system thus met our specifications for volumes from 5–250 mL in the series (see Figures 8 and 9).

Preparation for patient care

Between June 2016 and June 2017, 1342 preparations were produced (135 runs). On average, ten preparations per run were processed. Ten runs were excluded from the evaluation because they were not completed, either due to technical problems or errors by technicians. Depending on the daily number of prescriptions, staff and the molecules available on the automated system, between one and four runs were performed per 8 h working day.

Of all preparations, 47.8 % showed a weight deviation of < 1 % from the target dose, 37.3 % displayed a deviation from 1 %–3 %, 9.5 % deviated from 3 %–5 %, 3.66 % deviated from 5 %–10 % and 1.72 % of preparations were outside of our defined acceptable range, at > 10 % deviation.

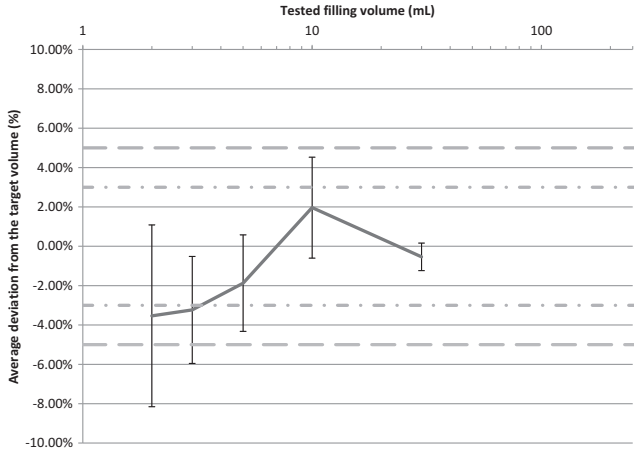

Figure 8: Filling accuracy (relative error ± 95% CI) of the PharmaHelp® automated compounder, individual doses of a viscous product carried out for performance qualification (9 batches of 4 IV bags, N = 36 IV bags).

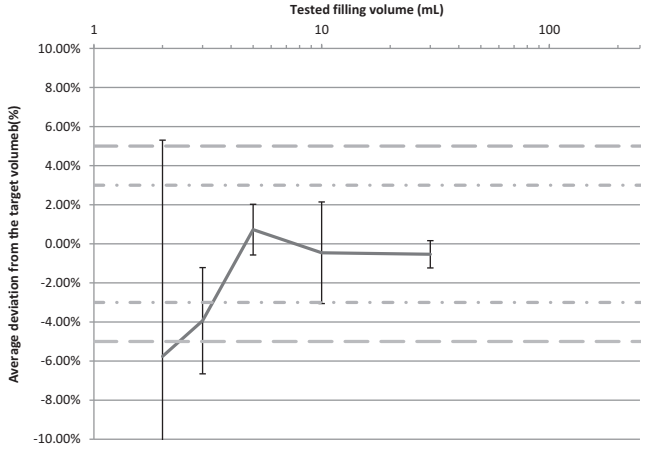

Figure 9: Filling accuracy (relative error ± 95 % CI) of the PharmaHelp® automated compounder, for a series (standard doses or dose banding) of a viscous product carried out for performance qualification (9 batches of 5 IV bags by tested volume, N = 45 IV bags).

Chemical contamination

Surface contamination

Neither volatilisation nor contamination of isolator surfaces was observed from the 90 bags produced. Only one contamination related to the operation of the automated system was detected. This was a very low contamination (spots < 3 mm) but a relatively frequent one (11 %). The contamination corresponded to the formation of a drop on the body of the needle when the robot withdrew the syringe and a low level of contamination of the septum at the injection port to the final bag was observed in some situations.

Following this experience, the pharmacy chose to place caps at the bag's injection septum and to install absorbent protection mats to prevent contamination in case of technician error.

Microbiological validation

No microbiological contamination (N = 90) in normal or worst case conditions was visible in any of the bags or vials, even after incubating for 7 days at room temperature and a further 7 days at 32.5 °C.

Productivity

Total average processing time was assessed as taking 61 min (95 % CI ± 11 min), including 16 min (95 % CI ± 5 min) for the automated production process (see Table 1). Because the manual pre-processing and post-processing steps can be performed while the automated production run of another batch is taking place, production time could be shorter still if more than one run were to be made, and this would create an efficiency gain. In comparison, the assessment of the manual gravimetric-based preparation of one bag (mean preparation time assisted by computerised gravimetric verification, in July 2016) and extrapolation to ten bags (mean preparation time for one IV-bag x10), as described above, led to a result of 63 min. The production steps alone (drug withdrawal from the vial and admixture into the bag) took 30 min.

Table 1: Average time for production of a batch of ten IV bags (N = 9 runs).

Type of process	Mean (± 95 % CI)	SD
Pre-process	18 min 30 s (± 1 min)	1 min 17 s
Process	16 min 40 s (± 5 min)	6 min 23 s
Post-process	20 min 35 s (± 5 min)	6 min 21 s
Time for production	55 min 44 s (± 11 min)	14 min 00 s
Time for production including robot-head initialisation	60 min 44 s (± 11 min)	14 min 00 s

Productivity differed according to admixing volume. The injection time measurement test revealed a linear relationship between the admixing volume and time (y = 72,879 x −233.27, R[2] = 0.9952). The admixing times for volumes from 2–1000 mL took from 5–23 min for ten IV bags.

Discussion

Few data are available on the qualification of automated systems for injectable cytotoxic compounding. The performance requirements of these emerging technologies are not defined by regulations. However, as pharmacists in industry would do, hospital pharmacists have to define the specifications of the end-product manufactured by the automated system in order to deliver a drug that complies with strict medical regulations and clinical needs. Using these data, pharmacists have to determine acceptability criteria and identify which essential checks are required to qualify the equipment to design a manufacturing process suitable for routine manufacturing. The automated system must consistently deliver a product that meets its predefined level of quality and clinical needs. The PharmaHelp® device is comparable to precision pump systems. We were therefore able to rely on standards for medical devices [10], particularly precision pumps, to qualify this chemotherapy drug production machine. The number of production repetitions necessary to obtain statistically significant results is still debated. However, the consensus in the field of equipment qualification is that a minimum of three repetitions should be performed and that they must all be within the set specifications to validate the test.

Electronic prescriptions were transferred to the pharmacy production software via an interface, and this method proved effective. An interface with an Enterprise Application Integration (EAI) linked to our prescription software offered a one-click transfer of selected production items and the possibility of switch between manual production, assisted by computerised gravimetric control (CATO®), and the automated system. In case of a problem, this allowed us to transfer the same prescription to another production process while maintaining full traceability.

Contamination due to the robot's activity was considered very low. It was limited to the injection syringe's needle and the IV bag's drug injection port. Contamination events such as spillage did occur during the quinine test of the PharmaHelp® device, but their main cause was a lack of attention and mistakes by technicians during loading—the robotised process itself was not involved. These vents were therefore not notified in the results.

The dose accuracy of the chemotherapies manufactured by the automated system was excellent, with an SD < 1 % for volumes from 5–250 mL and met with our specifications. These results would be better than those for manual preparation, where significant intra- and inter-technician variability in dose accuracy can be observed; the median deviation from target concentrations in manual preparation varied significantly ($p < 0.001$) from −6.5 % to 0 % [16]. These results confirmed those of the first studies on compounding robots [2, 6, 17].

For volumes from 2–5 mL, the automated system's accuracy was satisfactory but could be improved. The dose accuracy met with our specifications, except for viscous molecules. The automated system was less accurate for 2–250 mL volumes, and from 0 % to 2 % bag rejection was observed, depending on the run. Greater deviations

were mostly associated with the filling of the first IV bag in a drug run and/or with particular drugs like paclitaxel, irinotecan, cyclophosphamide, etoposide phosphate. This could be explained by the aspiration of an excessive dead-air volume into the filling syringe—despite a special suction needle (PharmaNeedle®) which prevents air being drawn up—and adjusting some software parameters, like the theoretical dead-air volume and the speed of syringe filling, may remedy this problem. There were multiple other possible causes: highly viscose drugs (e. g. irinotecan), very oily drugs (e. g. paclitaxel), and powdered or lyophilised drugs (e. g. etoposide), which first need to be reconstituted. Although potential solutions have been proposed for solving problems of inaccuracy with highly viscose and oily drugs (vials with two air intakes, slower syringe filling), how to deal with reconstituted drugs is still being studied (the possibility of using a dispensing pin with the automated system in the future). Nevertheless, since the first generations of chemotherapy compounding robots [18] the technology has made much progress in terms of accuracy and robustness, and it can now be used in daily practice.

Using the robot was simple and easy to learn, but required training and significant support for the pharmacy team at the beginning of its implementation [19]. The development of foolproof devices and alarms would improve the identification of any mistakes—alarms to inform the technician of a wrong or wrongly positioned receptacle, for example. Indeed, IV bags were not automatically checked during pre-processing, but scanning coupled to the balance is currently in development. Other problems were the choice and checking of IV tubing; no tubing check occurred with the robot despite some chemotherapy drugs requiring specific IV tubing: DEHP-free (paclitaxel), PC-free (busulfan), opaque (dacarbazine), with (pemetrexed) or without a 0.22 µm filter (albumin- paclitaxel). The automated compounding device has similar safety and traceability capabilities to computerised gravimetric checking (CATO®), but it seems to improve quality by decreasing dose variability, preventing musculoskeletal disorders [20] and reducing staff exposure [3, 4].

Although Seger and al [21]. showed that mean drug preparation time increased by 47 % on moving to a fully automated robotic approach from manual compounding, the automated PharmaHelp® system did not seem to waste or save time [6]. Time savings could be expected if several consecutive runs and standard doses were made involving only one drug. In this case, the device only requires one syringe and can prepare several admixtures with one withdrawal of the drug, limited only by the volume of the syringe (60 mL), and thus reducing the time necessary to compound ten bags. For this reason, the PharmaHelp system seems to be a very promising one for optimising the preparation of bags when dose-banding.

Setting up the vials, validating new molecules and training technicians took time and did not allow the robot to be used to its full potential immediately. In addition, production directly into syringes and infusers still requires development and is not currently possible. Nevertheless, the number of chemotherapies prepared in our pharmacy increases every month.

Conclusion and perspectives

Qualifying an automated system for the preparation of injectable cytotoxic drugs required the verification of several important points: the microbiological safety and accuracy of the doses delivered are particular weak points in the process, which could lead to misuse or a safety failing. The qualification process was complex and time- and resource-consuming; however, it was, of course, mandatory to ensure the safe use of this device.

The automated PharmaHelp® system, in its biosafety cabinet version, was capable of producing antineoplastic drugs of an appropriate product quality and safety, as well as ensuring optimal protection for staff (less exposure and fewer musculoskeletal disorders) and the environment (low contamination). The qualification validation of a robot is time-consuming. It needs the equivalent of a full-time person for three weeks for tendering and two pharmacists at 50 % and two technicians at 20 % for one year.

However, significant technician training is necessary for the proper functioning of this type of equipment. Productivity gains were only proven in the case where several consecutive runs were produced. The present study concludes that the automated PharmaHelp® system seems to be most efficient and suitable for the preparation of dose-banded drug doses for volumes from 2–250 mL with non-viscous solutions and for volumes from 5–250 mL with viscous solutions. Thus, a benefit for the use of the dose-band can be expected in terms of productivity and return on investment, but a study must be conducted in real working conditions to confirm these assumptions. This emerging technology is undeniably promising, even though it still requires developments that can offer broader production possibilities (syringes and infuser pumps).

Conflict of interest statement: The authors state no conflict of interest. The authors have read the journal's Publication ethics and publication malpractice statement available at the journal's website and hereby confirm that they comply with all its parts applicable to the present scientific work.

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