

## Safety features of manual and automated process for preparing cytotoxic dose – mapping the differences

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### ABSTRACT

**Study objectives:** A cytotoxic compounding robot was installed in two European hospital aseptic units, UK and Italy. Currently, the effect of automation on the safety aspects of cytotoxic dose preparation is unknown. The objective of this study was to compare the manual and automated cytotoxic preparation processes to better understand the safety features associated with each.

**Methods:** Process maps of manual and automated processes for preparing a single dose were produced. Numbers of manual steps, total steps and accuracy check steps were compared. Differences between manual and automated process were described. The effect of automated batch preparation (eight doses) was also evaluated at the UK site by comparing the process maps.

**Results:** There was no difference in the number of manual steps between the two processes for preparing a single dose. Automation led to five additional steps in total. Some manual steps in the automated process were less complex than with the manual process. For batch preparation, automation reduced the total number of manual steps by 42 and required 30 fewer steps for the overall process. Automation increased the number of accuracy checks by three to twelve steps (13–20%), depending on the site and number of doses prepared.

**Conclusion:** Our findings suggest that automation has the potential to increase safety by reducing the complexity of manual tasks and introducing more objective accuracy checks. However, the effect was influenced by how automation was integrated within existing systems.

### KEYWORDS

Compounding, cytotoxic, robot, safety, technology

### INTRODUCTION

It is widely recognised that cytotoxic dose preparation is a complex and hazardous process. Manual preparation of a cytotoxic dose involves a number of preparatory steps including screening, labelling, assembly of materials and compounding. Given the cytotoxic nature of the drugs,

stringent precautions must also be followed to minimise operator exposure, and accuracy checks must be performed to safeguard patients against errors in the production process. One of the challenges for hospital pharmacy aseptic units is to provide a timely, flexible, safe and accurate cytotoxic production service.

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As in many other areas of health care, technological advances are being developed to help deliver safer and more efficient care to patients worldwide. In 2007, a cytotoxic compounding robot (CCR; CytoCare) was installed and evaluated in three European hospital pharmacy aseptic units as part of a multicentre market validation study funded by the European Commission [1]. The CCR uses a combination of robotics, bar code recognition and camera-image recognition technology to prepare cytotoxic doses, thus minimising the manual handling of cytotoxics by operators [2]. Communication with the CCR is performed using the associated software, which provides the platform for an operator to instruct the CCR on the cytotoxic doses to be produced, as well as maintaining a record of all doses made.

As might be expected, the implementation of the CCR has changed the way in which pharmacy aseptic staff prepare

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cytotoxic doses and consequently how the service is managed within the units. For example, the CCR can handle up to eight doses at any one time and as a result, a batch of eight patient-specific doses of different drugs can be manufactured in one compounding cycle. Similarly, prior to CCR compounding, raw materials can be batched instead of being assembled separately. In comparison, a typical manual process produces one patient-specific dose at a time. Furthermore, there are a number of automated accuracy checks within the CCR including the use of drug-specific gravitational weight checks to verify the accuracy of volumes withdrawn from a vial of drug or diluent.

However, while there is a number of potential safety benefits associated with such automation, there may also be an increased risk of errors that may not at first be apparent. Statistically, for any given process, the probability of performing perfectly may be determined by the product of success at each step of the process, see Table 1 [3]. It follows that the greater the number of steps in a process, the higher the potential risk of error. There is a balance between optimising the number of opportunities for error by reducing the number of steps, and removing a step that might compromise the safety or accuracy of the process.

The aim of this study was to compare the manual and automated cytotoxic preparation processes in two European hospital pharmacy aseptic units, one in the UK and one in Italy, in order to understand the risks and safety features associated with each. Our objectives were to compare: 1) the number of manual steps; 2) the total number of steps; and 3) the number and type of accuracy checks (whether manual or automated) between the manual and automated processes.

## METHODS

### Setting

Both of the aseptic units studied provided a hospital pharmacy aseptic service typical of the country concerned, with approximately 15,000 parenteral cytotoxic doses produced per annum on each site. The UK pharmacy aseptic unit was a licensed unit regulated by the UK Medicines and Healthcare Products Regulatory Agency and the Italian pharmacy aseptic unit was regulated by the hospital microbiology department.

At both sites, cytotoxic doses were prepared in syringes or infusion bags, as well as other infusion devices, by trained and validated operators. The same CCR was installed at each study site, described in full on the

**Table 1: The probability of performing a process perfectly (adapted from Botwinick et al. 2006)**

Number of steps	Probability of success for each step in the process		
	0.95	0.99	0.999
1	0.95	0.99	0.999
10	0.60	0.90	0.990
20	0.36	0.82	0.980
50	0.08	0.61	0.951
100	0.01	0.37	0.905

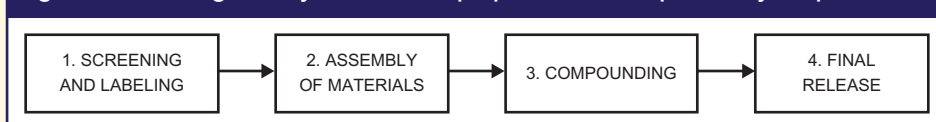
manufacturer's website [2]. At the time of the study both sites were concurrently using both manual and automated processes, depending on the cytotoxic drugs involved. The study sites differed in their aseptic unit layouts, equipment and consequently their workflow processes. For example, at the UK site, cytotoxic doses were compounded in two areas: an International Organization for Standardization (ISO) 7 room (equivalent to European Good Manufacturing Practice (EU GMP) Grade C environment) within which an isolator was located, and an ISO 5 room (EU GMP Grade B) where the CCR was located. At the Italian site, all clean air devices (two laminar flow cabinets, laminar flow cabinets (LFCs) and one CCR) were located in an ISO 7 room (EU GMP Grade C). The difference in room environment between the two sites reflected standard practice at each unit. This in turn affected the level of access in each area with respect to the protective clothing and training required, and workflows at each site. However, irrespective of the room classification, the isolator, LFC and CCRs within the units were all validated to provide an ISO 4.8 (EU GMP Grade A) environment. Both study sites were compliant with the EU GMP guidelines [4-6].

### Manual process for cytotoxic dose preparation

Cytotoxic doses were prepared in four stages, see Figure 1.

Stage 1. Each chemotherapy order received in the pharmacy aseptic unit was screened by a pharmacist responsible for assessing clinical appropriateness of the doses prescribed. At the UK site, the pharmacist screened a paper chemotherapy order. Once approved, the patient and chemotherapy order details were manually entered into

**Figure 1: Four stages of cytotoxic dose preparation in the pharmacy aseptic unit**



the pharmacy computer system by a pharmacy technician or pharmacy assistant. From this computer system, labels and a manufacturing worksheet (a standard form comprising a unique batch number, list of raw materials required and compounding instructions) were produced. At the Italian site, pharmacists screened an electronic chemotherapy order and labels were printed directly from the same computer system by a pharmacy technician.

Stage 2. The next stage involved assembly of the raw materials such as the drugs and diluents, which were then transferred to the clean air device by either a pharmacy assistant or pharmacy technician for manual compounding. At the UK site, the raw materials were checked by a second pharmacist or pharmacy technician for accuracy of raw material selection, worksheet documentation and accuracy of details on labels before the materials were transferred for compounding. At the Italian site, assembly was carried out in the same room as the LFC; all raw materials required were visually inspected by a pharmacy technician for accuracy of selection and transferred directly to the LFC for compounding.

Stage 3. At the compounding stage, a pharmacy technician manually reconstituted and/or diluted the drug before injecting the appropriate volume into a final container such as a syringe or infusion bag ready for administration. This stage was the same at both sites and the number of manipulations was dependent on the drug and dose required.

Stage 4. Once compounding was complete, a pharmacy technician removed the cytotoxic dose from the isolator/LFC and transferred it out of the clean room at the UK site, or placed on a workbench at the Italian site. The dose was then visually inspected by a pharmacist or a second pharmacy technician for particulate contamination before being packaged and stored for collection by ward staff. At the UK site, a pharmacist or pharmacy technician also cross-checked the dose against the manufacturing worksheet to reconcile the labels and materials.

#### *Automated process for cytotoxic dose preparation*

The use of the CCR resulted in a number of changes to the cytotoxic dose preparation process.

Stage 1. Following the same screening and approval steps as the manual process, details of each cytotoxic dose were manually entered into the CCR software at the UK site by a pharmacy technician. The details were verified by a second pharmacist or pharmacy technician who was also responsible for scheduling approved doses into batches of eight for automated compounding and producing

a picking list. Batch processing was used as the robot was placed in a dedicated ISO 5 (EU GMP Grade B) room which required additional gowning prior to compounding. At the Italian site, there was a direct interface between the pharmacy computer system and the CCR software. This meant that there was no transcription step. The CCR was also located in the same room as the computer and raw materials; therefore no additional gowning was required and each cytotoxic dose could be set up and prepared individually. Consequently, batch preparation was not studied at the Italian site. Once the chemotherapy order had been screened as for the manual process, a unique bar code label for tracking the final container of each dose was printed at both sites by a pharmacist or pharmacy technician.

Stage 2. At the UK site, raw materials were batch assembled and documented by a pharmacy technician, then transferred to the clean room where the CCR was located. At the Italian site, raw materials for each cytotoxic dose were assembled separately by a pharmacy technician. A unique bar code label was attached to each final container at both sites.

Stage 3. At both sites, a pharmacy technician (and/or pharmacy assistant at the UK site) loaded assembled materials into the CCR which automatically confirmed the identity of the materials using a combination of bar code scanning and image-recognition technology. The CCR automatically compounded each cytotoxic dose scheduled (UK site: batch of up to eight doses; Italian site: single doses). The volume of drug used was verified using drug-specific gravitational weight checks. This was performed by weighing each drug vial before and after the required volume was removed. After each cytotoxic dose was compounded, the syringe or infusion bag was placed on a carousel ready for removal by the pharmacy technician.

Stage 4. At both sites, a second pharmacy technician or pharmacist visually inspected each dose for particulate contamination and scanned their bar codes to confirm completion of the preparation process on the CCR software. Labels were produced from the CCR software and attached to each final dose before being packaged for storage or collection by ward staff. At the UK site, there was an additional step where a pharmacist or pharmacy technician cross-checked the details of each dose entered in the CCR software against the prescription for accuracy of documentation.

#### **Production of process maps**

The manual and automated processes at each site were mapped for each of the four stages of the cytotoxic dose

preparation process. Each map started at the prescription screening stage and ended once the cytotoxic dose was released and packaged. A single expert panel comprising staff from both sites: two pharmacy aseptic managers, one aseptic services pharmacist, one pharmacy technician and two research pharmacists piloted and developed a set of definitions for the process maps. For each map, a process step was defined as a step where one or more of the following opportunities for error may occur: error in the content of the cytotoxic dose prepared, error in labelling, error in documentation. Each step was further classified as a manual step if it was performed by an operator, or an automated step if the step was performed by the CCR or associated software. A step that involved documentation of an accuracy check, either manually by an operator or automatically by the CCR, was also classified as accuracy check step (manual check or auto check respectively). At both sites, all processes were carried out according to local standard operating procedures.

At the UK site, the process maps and associated level of granularity were agreed through an iterative process of direct observation and discussion with pharmacy aseptic staff. At the Italian site, process maps were produced through discussion and iteration only. All maps were produced to the same level of granularity to enable comparison of process steps and the face validity of the maps were confirmed by two pharmacy aseptic staff familiar with both processes at each site.

## Data analysis

For the preparation of a single dose, we counted and compared the following for each process map: number of manual steps, number of automated steps, total number of steps, number of steps which were manual accuracy checks and number of steps which were automated accuracy checks. A second set of comparisons were made by comparing the number of steps required to prepare a batch of eight cytotoxic doses at the UK site.

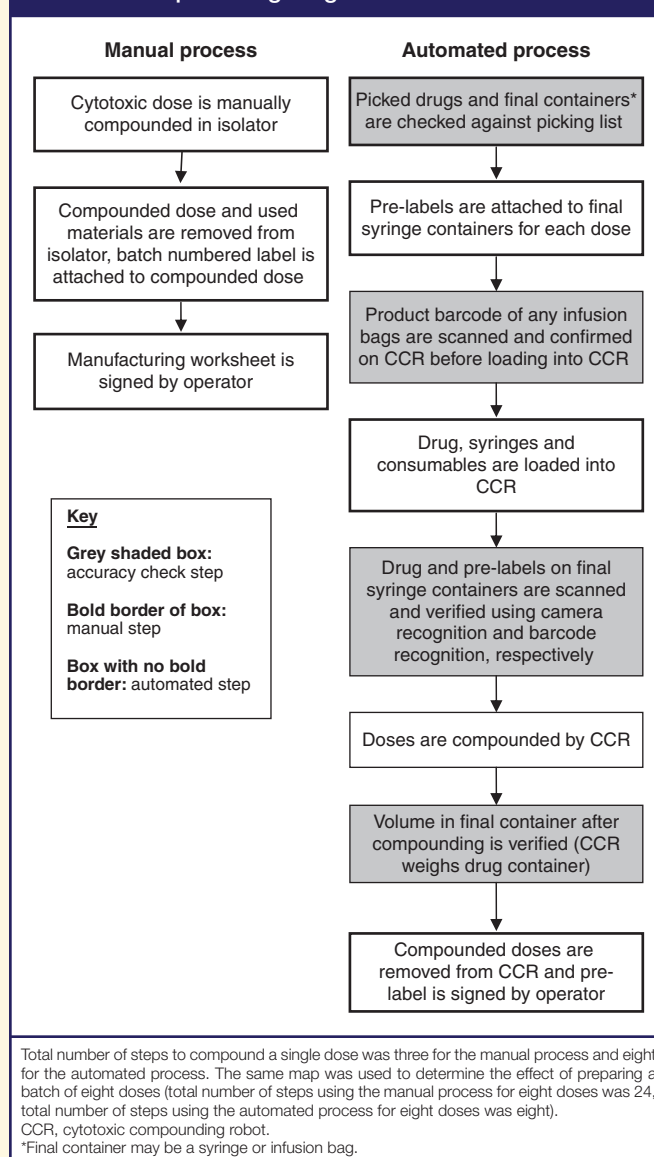
## RESULTS

Manual and automated process maps for both study sites were produced and finalised in October 2010. An example map of the preparation stage (stage 2) at the UK site is given in Figure 2. Full process maps may be obtained from the authors.

### Manual steps

The number of manual steps counted in the process maps are presented in Table 2. For preparing a single cytotoxic dose there was no difference in the number of manual steps between the manual and automated processes at either site. For preparing batches of eight doses, batching at the

**Figure 2: Process steps for manual and automated compounding stage at the UK site**



assembly of materials and compounding stages contributed to an overall reduction of 42 manual steps in the automated process at the UK site. Example changes in process steps at the compounding stage are shown in Figure 2.

### Total number of process steps

Automation led to an increase of five automated process steps in total to prepare a single dose compared with the manual process at each site, see Table 3. For preparing batches of eight doses in the UK, the use of automation required 30 fewer steps in total compared to the manual process (equivalent to a reduction of 25% in the number of process steps).

**Table 2: A comparison of the number of manual steps to prepare cytotoxic dose(s) between the manual and automated processes**

Stage	Single Dose (UK)		Eight doses (UK)		Single dose (Italy)	
	Manual process	Automated process	Manual process	Automated process	Manual process	Automated process
1. Screening and labeling	4	5	32	33	3	2
2. Assembly of materials	4	1	32	1	2	2
3. Compounding	3	4	24	4	4	4
4. Final release	4	5	32	40	2	3
Total number of manual steps	15	15	120	78	11	11

### Accuracy checks

There were three to twelve more accuracy check steps with the automated process than the manual process, depending on the number of doses prepared, see Table 4. At the UK site, the manual check of patient's details, dose, labels and raw materials against the compounding worksheet prior to compounding was split into two manual check steps in the automated process; one manual check to confirm the transcription of patient and prescription details on to the CCR software, and one manual check of raw materials against picking list prior to loading into the CCR. At the Italian site, manual check of the label on the final dose was done using automation instead. Four new auto checks were introduced at each site following the use of the CCR. Three of the four auto checks were at the compounding stage where the product bar-code or pre-label of final container was scanned; the drug vial was cross-matched with library images to confirm identification using camera-recognition technology and automated verification of volume used by drug-specific gravitational weight checks. The fourth auto check involved bar-code scanning the pre-label at the final release stage.

**Table 3: A comparison of the total number of manual and automated steps to prepare cytotoxic dose(s) between the manual or automated processes**

		UK		Italy	
		Manual process	Automated process	Manual process	Automated process
Single dose	No of manual steps	15	15	11	11
	No of automated steps	0	5	0	5
	Total	15	20	11	16
Eight doses (batch handling)	No of manual steps	120	78	Not applicable	
	No of automated steps	0	12		
	Total	120	90		

### DISCUSSION

#### Key findings

Based on our analysis of manual and automated processes in two European hospital pharmacies, we found automation was associated with: 1) the same number of manual steps; 2) an increase in the overall number of process steps (manual and automated combined); and 3) an increase in the number of accuracy check steps, to prepare a single dose. For preparing a batch of eight doses at the UK site, we found automation was

associated with: 1) fewer manual steps; 2) fewer process steps overall; and 3) a greater number of accuracy check steps.

#### Safety features of manual and automated cytotoxic dose preparation

There is some evidence that automation can increase safety in health care [7, 8], however, this has not been explored in the area of cytotoxic compounding. Based on the statistical probability of performing perfectly we have compared the number of steps required in both the manual and automated cytotoxic preparation process. Although there were a number of differences in workflow between the two sites, the effect of automation was largely the same.

For preparing a single dose, the total number of steps was greater in the automated process than manual process which suggests there may be more opportunities for error with the automated process. However, the number of manual steps to prepare a single dose was the same and therefore the number of opportunities for human error would appear to be the same. When one considers the changes in the type of process steps, our findings suggests something different. The automated process may be safer as: 1) the manual steps were generally less complex in the automated process than in the manual process, e.g. loading materials into CCR for automated compounding compared with manual manipulations to compound each cytotoxic dose; 2) the multiple manual manipulations required to compound a dose was counted as one step

**Table 4: A comparison of the number of accuracy check steps cytotoxic dose(s) in the manual and automated processes**

Number and type of accuracy checks (percentage of total number of steps)		UK		Italy	
		Manual process	Automated process	Manual process	Automated process
		n = 15	n = 20	n = 11	n = 16
Single dose	Manual checks	3 (20%)	4 (20%)	2 (18%)	1 (6%)
	Auto checks	0	4 (20%)	0	4 (25%)
	<b>Total</b>	<b>3 (20%)</b>	<b>8 (40%)</b>	<b>2 (18%)</b>	<b>5 (31%)</b>
Eight doses (batch handling)		<b>n = 120</b>	<b>n = 90</b>	Not applicable	
	Manual checks	24 (20%)	25 (28%)		
	Auto checks	0	11 (12%)		
	<b>Total</b>	<b>24 (20%)</b>	<b>36 (40%)</b>		

in the manual process instead of counting each individual manipulation as separate steps; and 3) there were more accuracy check steps in the automated process than manual process.

In a complex process such as the preparation of a cytotoxic dose where a number of different staff are involved, accuracy checks are an essential part of the system to ensure that the correct cytotoxic dose is prepared. Our study found that the number and proportion of accuracy checks were higher in the automated process thereby suggesting that any errors made would be more likely to be detected in the automated process. Exploring this further, each check step may be analysed according to the type of content checked, and the method of check (manual or automated).

Based on the type of content checked at the UK site, the manual check of patient's details, dose, labels and raw materials against the compounding worksheet prior to compounding was split into two manual check steps in the automated process; one manual check to confirm the transcription of patient and prescription details on to the CCR software, and one manual check of raw materials against picking list prior to loading into the CCR. These changes were made as the automated process produced less paperwork; raw materials for multiple doses were produced on a single picking list without the need for individual patient details and there were no compounding instructions produced. Consequently, a transcription check was introduced for each patient dose entered on the CCR software to ensure the correct details had been entered, and a separate check of raw materials was made afterwards. At the Italian site, the introduction of a CCR enabled each final dose to be checked using automation and therefore the equivalent check in the manual process was no longer required.

From comparing the method of accuracy check steps between the two processes, there were four new auto checks in the automated process. Three of these were at the compounding stage where accuracy is particularly important to ensure the right dose is made. This included an automated volume check based on the specific-gravity of the drug used which should be more precise than a visual volume check. Overall, by taking into account the changes in type of process step in addition

to the number of process steps, we were better able to assess and compare the relative safety of the manual and automated process.

### Batch preparation

When using batch preparation at the UK site, the potential safety benefits were more apparent than that for the preparation of a single dose. In addition to the safety features of the automated process discussed, the total number of process steps was reduced by 25% from the manual process which means there were fewer potential opportunities for error. However, much of the benefit for batch preparations is dependent on the workflow at the aseptic unit concerned. At the UK site, batch preparation was preferred as the robot was placed in a dedicated ISO 5 (EU GMP Grade B) room. This meant that the operator must have all the raw materials prepared before they gown up and enter the clean room. At the Italian site, the CCR was in the same room as the computer and raw materials, therefore no additional gowning was required. Each cytotoxic dose could be set up and prepared individually. Thus, although batch preparation appeared to be beneficial at the UK site for reducing the total number of process steps and the opportunity for error (without reducing the number of accuracy checks), we have not advocated batch preparation at the Italian site as it may create unnecessary delays in dose preparation.

### Limitations

Process mapping is a relatively subjective method that results in a simplified model of events in practice. To minimise such subjectivity, we developed and applied a user-derived definition of a process step, had an expert panel confirm the face-validity of our process maps and produced our maps to the same level of granularity to allow comparisons to be made. This included the decision to

model compounding as a single step. The complexity and variation of manipulations required during compounding meant that the number of opportunities for error within this step was unpredictable. Further, in creating a simplified model, we omitted a number of steps in the cytotoxic preparation process, e.g. standard cleaning procedures, gowning requirements, operator training and validation. These were likely to have an impact on the duration of the process and staff skill mix but were outside the scope of the present study.

We have suggested that automation is likely to have fewer opportunities for error than the manual process and that any errors made would be more likely to be detected as there are more accuracy checks in the automated process at both pharmacy aseptic units. However, the performance of the CCR is governed in part by human operators involved in the maintenance and input of data. Consequently, the benefits of automation may only be realised if new potential risks are managed and the technology is used appropriately. In other words, a single human error at the system level, such as incorrect calibration of the electronic weighing scales, could result in multiple errors at the compounding stage and batch processing may not be a more efficient method than single dose preparation in some units.

We did not collect any data on any errors that occurred in practice with either the manual or automated process. Although process mapping was a useful and practical method for our study, our findings cannot be used as evidence that the use of a CCR will decrease errors in the

cytotoxic preparation process or reduce the likelihood of releasing an inaccurate dose for administration to the patient. Finally, we were unable to compare our findings with other CCRs due to the lack of published literature in this relatively new and innovative area. Our objective was to compare the differences in safety features between the manual and automated process and we have achieved this using process mapping. By studying the workflow in two different pharmacy aseptic units, we have identified a number of differences in safety features which may be of use to other pharmacy aseptic units looking to implement a CCR.

## CONCLUSION

In this study, we have described the differences between the manual and automated cytotoxic dose preparation in two pharmacy aseptic units in two European countries. Our analysis suggests that our automated compounding process has the potential to increase safety by reducing the complexity of manual tasks such as compounding and introducing more objective automated accuracy checks by using bar code scanning, image-recognition and drug-specific weight checks. Based on our study in two hospital pharmacy aseptic units in two European countries, we found the effect of automation on safety was influenced by how automation was implemented within existing systems and workflows.

Further investigations are required to confirm the potential benefits of automation for reducing the risk of preparing inaccurate cytotoxic doses and preventing their release for administration to the patient.

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