Cytotoxic surface contamination in a robotic system in comparison to manual compounding

Introduction
The preparation of cytotoxic drugs involves the occupational risk of contamination by aerosolized drug product or contact contamination. Some of these drugs are known to be carcinogenic, mutagenic or teratogenic in humans, therefore the operator exposure should be kept as low as possible. To work with a robot could be an option to reduce the operator’s risk, however, some previous works showed that the contamination with cytotoxic drugs during automated preparation could be similar or higher than during the manual preparation.

The main goal of this study was to compare the surface contamination with cytotoxic drug substances during automated preparation and during the manual preparation process.

Material and Method
The contamination level of 5 predetermined areas with a possible high risk of contamination inside the Apoteca™ cabinet was investigated with swab tests, according to a known method [Schierl R, et al.]. In the first series, 15 bags of 5-FU and 15 bags of platinum containing cytotoxic drugs were prepared during two consecutive days:
- 15 x 5-FU 1200 mg ad 500 ml (day 1)
- 5 x cisplatin 40 mg ad 500 ml (day 2)
- 5 x carboplatin 450 mg ad 500 ml (day 2)
- 5 x oxaliplatin 120 mg ad 500 ml (day 2)

All surfaces were swabbed before and after the preparation process and in addition the outer surface of each bag was swabbed.

In parallel, the surface contamination during the manual preparation was studied. 15 bags of 5-FU and 15 bags of platinum containing cytotoxic drugs were prepared during two consecutive days.

Four specific areas of the laminar air flow, the gloves of the technician and all bags prepared were swabbed by the same method.

5-FU suspect samples were analysed by gas chromatography / mass spectrometry and platinum suspect samples were analysed by voltammetry after UV-digestion according to a known method [Schierl R, et al.].

Results were evaluated with Threshold Guidance Values. [Schierl R, et al.]

Results and discussion

Contamination in the Apoteca™ cabinet

<table>
<thead>
<tr>
<th>Place of sampling</th>
<th>5-FU (pg/cm²)</th>
<th>Platinum (pg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance (ca. 45 cm²)</td>
<td>2.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Floor under the shelves (ca. 270 cm²)</td>
<td>2.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Syringes / Holder (ca. 400 cm²)</td>
<td>1.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Robotic arm (ca. 180 cm²)</td>
<td>1.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Blank value</td>
<td>2.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Balance (ca. 45 cm²)</td>
<td>0.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Floor under the shelves (ca. 270 cm²)</td>
<td>1.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Syringes / Holder (ca. 400 cm²)</td>
<td>1.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Robotic arm (ca. 180 cm²)</td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>

Contamination in the Laminar Air Flow workbench

<table>
<thead>
<tr>
<th>Place of sampling</th>
<th>5-FU (pg/cm²)</th>
<th>Platinum (pg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP light (ca. 400 cm²)</td>
<td>3.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Preparation meds compounding (ca. 400 cm²)</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Preparation meds vials (ca. 266.5 cm²)</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>AP light (ca. 400 cm²)</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Preparation meds compounding (ca. 400 cm²)</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Preparation meds vials (ca. 266.5 cm²)</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>AP light (ca. 400 cm²)</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Preparation meds compounding (ca. 400 cm²)</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Preparation meds vials (ca. 266.5 cm²)</td>
<td>1.3</td>
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</tr>
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<tr>
<td>Preparation meds vials (ca. 266.5 cm²)</td>
<td>1.3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Cytoxic contamination was observed in the working area of Apoteca™ and on the outer surface of several products automatically compounded.

The contamination levels were similar or lower during robotic preparation in comparison to manual preparation.

Conclusion
The key parameters to reduce a cytotoxic surface contamination with an automated robotic system for chemotherapy compounding are the adjustments of the robotic arm.

In addition, a good and reliable cleaning method needs to be regularly performed in order to remove thoroughly the potential surface contamination.

Reference
Accuracy of preparations compounded by a robotic system in comparison to manual compounding

Introduction

In antineoplastic chemotherapy, the accuracy of preparation interferes with the patient safety. Accuracy of manually compounded preparations depends on the skills of the operator and the precision of the devices used as the operator prepares the dose by volumetric measures. A robotic system, performing gravimetric controls, could improve accuracy and consequently patient safety, when assuming that the accuracy of the preparations automatically compounded is better than those compounded manually.

The main goal of this study was to compare the accuracy of preparations compounded by an automated robotic system (Apothece™) with preparations compounded manually.

Material and Method

For automated compounding with Apothece™, 3 types of syringes with different sizes (3 ml, 10 ml and 50 ml) are stipulated. 8 different doses (1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml, 3.0 ml, 10.0 ml, 10.5 ml and 50.0 ml) of sterile water were added to 250 ml bags prefilled with 0.9 % NaCl solution. For each dose, 10 bags were compounded. All bags were weighed before and after compounding on an external balance with a precision of 0.01 g.

In parallel, bags with the same nominal doses were prepared following standard manual procedures:
- In the first series, the same types of syringes like in the robot were used (3 ml, 10 ml and 50 ml).
- In the second series, syringes were used in accordance with the standard operating procedures of manual compounding in our facility (1 ml, 2 ml, 3 ml, 10 ml, 20 ml and 50 ml).

The precision was calculated as percentage rate of the deviation of the nominal value.

Results and discussion

Automated compounding with Apothece™

None of the bags compounded with Apothece™ during this study failed with accept limit for precision set as ± 5 %

Conclusion

The accuracy of robotic preparation with Apothece™ is highly acceptable compared to manual preparation.
THE FIRST TOTALLY ROBOTIZED LABORATORY FOR CYTOTOXIC DRUGS

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BACKGROUND
The Oncology Pharmacy of the University Hospital of Ancona (Italy) began a process of robotization of its laboratory five years ago after an agreement of collaboration with Loccioni Group that manufactures automated system for compounding cytotoxic drugs (APOTECChem). Before the use of robot our laboratory worked with two laminar air flow cabinet that usually produced about 20-22000 oncology preparation every years. After the introduction of the first automated system, the work was gradually transferred to the robot and one laminar air flow cabinet was disused. Then the robot increased a lot its capacity and the arrive, at the end of 2009, of a new machine allow us to think a new kind of laboratory where the robots are the principal way of compounding and the manual handling under a laminar air flow cabinet is only a minimal portion of the total work. This were the first example of totally automatized laboratory for preparation of anticancer drugs. The new objectives we established were 1) to cover more than 85% of total production with robots 2) to maintain unchanged the delivery time to the administration units.

This work shows the impact of the robotized pharmacy in the oncology workflow, together with the results reach along the years.

MATERIAL AND METHOD

RESULTS
The preparations compounded with the robots were 16200 in 2010 and 19300 in 2011. Actually in the first three months of 2012 we produced 4980 bags of therapies and we expect to overcome 20000 preparations delivered by the end of 2012. Our yearly workload was exactly 20220 preparation in 2010 and 20680 in 2011, so we covered with robotics respectively 80% and 93% of all the whole activity. In some days, we produces robotic production overcame 96% of workload.

The delivery time has not increased, on the contrary thanks to the integration between APOTECChem and the oncology medical record, the overall waiting time decreased of about 15%.

The automated production of the cancer therapies represents a big leap forward in the safety of patient and operator, thanks to the verification and traceability of each preparations, and to the confinement of the hazardous activities. We are confident this technology is going to represent the standard for the oncology pharmacy in the near future.

CONCLUSION

Data were obtained from the robot database. An other advantage of automation is related to the data mining. Every step is measured and traced, providing a huge amount of information helpful for both performance statistics and process re-organization.
ASSESSING SURFACE AND CROSS CONTAMINATION AFTER AN INTENSE USE OF A ROBOTIC SYSTEM FOR THE CHEMOTHERAPY COMPOUNDING

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BACKGROUND

The verification of chemical contamination is a fundamental requirement to ensure the safety of operator and patient. Robotic systems are designed to minimize the risk of chemical and microbial contamination. The main source of chemical contamination turns out from the cytotoxic drugs handling and depends mainly on the working procedures applied. In this work, we wanted to evaluate the level of environment contamination and cross-contamination generates during a thorough use of the robotic system.

MATERIAL AND METHOD

Fluorescein was chosen as marker for the chemical contamination verification due to its high fluorescence that, analysed by means of chromatography (HPLC with fluorimetric detector), allows the detection of minimum traces (LOD=1ppb). The protocol provided for the simulation of hospital pharmacy day activity, including the worst case conditions. Drug-like fluorescein vials at 1mg/ml concentration in NaCl 0.9% solution were used in different vial formulations: single-dose and multidose liquid solution, powder. Wipe tests were carried out at the end of the activity, without performing any cleaning procedures, and involves surfaces of the inner chambers of APOTECahemo, external surface of the compounded bags, touch-screen monitor, handle of the barcode scanner. The cross contamination is verified by detecting the marker inside test preparations compounded simultaneously with those having the tracer, but compounding only NaCl 0.9%.

Finally, the data were analysed using the Sessink’s threshold, the first based on healthcare safety considerations. The study correlates the contamination level of the urine samples of healthcare workers with that of the related surfaces.

RESULTS

None of the surfaces sampled outside the robot showed contamination (values < LOD), including the external surfaces of the bags compounded. As expected, low levels of contamination (between 0.02 and 0.06 ng/cm²) were recorded in some internal surfaces of the compounding room. These positive samples are well below the safety limit identified by Sessink. Concerning the cross contamination, no detectable traces of fluorescein were recorded either inside or outside the "control" bags without the marker, but compounded simultaneously with those having it.

CONCLUSION

A systematic protocol to assess drug contamination was designed and carried out. No relevant contamination was recorded after a massive amount of drug reconstituted. This work represents the first step to point out that robotic compounding can be considered as a safe level for environmental and cross contamination. Next steps provide for extending this approach to cytostatic drugs, such as fluorouracil and cyclophosphamid.

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Threshold Guidance Values for environmental contamination with cyclophosphamide (CP), [2]

<table>
<thead>
<tr>
<th>Test Surfaces</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual Liquid/Unscrew area</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Automated reconstitution area in robotic system</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Internal parking of the compounding area</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Robot electronic gripper</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Surface under the dosing device</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Dosing device</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Shade</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Internal surface of the dosing device</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Rod of powder reconstitution mixer</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Docking area of the robotic system</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Touch-screen monitor</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Handle of the manual barcode reader</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
<tr>
<td>Clean-up adapter for bags and electronic pump</td>
<td>&lt;0.01 ng/cm²</td>
</tr>
</tbody>
</table>

Test: Final products Result
14 Internal volume of bag 8 (cycle 7) <0.01 ng/ml
15 Internal volume of bag 10 (cycle 14) >0.01 ng/ml
16 Internal volume of bag 18 (cycle 18) >0.01 ng/ml
17 Internal surface of bag 1 >0.01 ng/ml
18 External surface of bag 2 >0.01 ng/ml
19 External surface of bag 3 >0.01 ng/ml
20 External surface of bag 4 >0.01 ng/ml
21 External surface of bag 5 >0.01 ng/ml
22 External surface of bag 6 >0.01 ng/ml
23 External surface of bag 7 >0.01 ng/ml
24 External surface of bag 9 >0.01 ng/ml
25 External surface of bag 10 >0.01 ng/ml
26 External surface of bag 11 >0.01 ng/ml
27 External surface of bag 12 >0.01 ng/ml
28 External surface of bag 13 >0.01 ng/ml
29 External surface of bag 14 >0.01 ng/ml
30 External surface of bag 16 >0.01 ng/ml
31 External surface of bag 17 >0.01 ng/ml

References:
[1] 36 preparations (14 syringes, 18 bags and 4 electronic pumps), using 23 ready-to-use solution vials (both single and multidose) and 14 powder vials.
RISK ASSESSMENT OF CYTOTOXIC COMPOUNDING: MANUAL vs ROBOTIC

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BACKGROUND AND PURPOSE
Errors in cytotoxic drug compounding can cause serious harm to patients due to the low therapeutic ratio. In a previous study, the prescription and the administration errors were reported as the main causes of medication errors in the oncology workflow. However, no data related to the manipulation phase were shown, likely due to the lack of verifications in the routine that makes errors difficult to detect. Robots are intended to decrease the risk of medication errors through 100% verification and traceability of the entire production process. This work is aimed at assessing the risk of medication errors in manual and automated compounding, taking into consideration the procedures and controls applied in both cases.

MATERIAL AND METHOD
The FMECA technique was applied to the procedures for the manual compounding defined in the Recommendations of the Italian Ministry of Health and to the compounding procedures of the APOT&AChemo robot. The analysis involved two Oncology Pharmacies working with automation in daily routine since 2007 and 2011 respectively. 5 macro-failure modes for the compounding process were identified and the corresponding Priority Risk Indexes (PRI) were calculated:
- labelling: sticking the final preparation with the wrong label;
- wrong drug: picking and compounding the incorrect drug;
- wrong dosage/dilution: transcription and administration of a wrong quantity of drug or drug dilution;
- wrong solvent: dilution of drug in the erroneous solution;
- contamination: accidental drug spillage.

RESULTS
The failure modes that show higher benefits in risk mitigation are the wrong drug and wrong dosage with a PRI decrease of 80% (from 50 to 10). Indeed the redundant controls (vision system, scale, photocells) on the loaded vials guarantee the compounding of the right drug. In addition, the drug is dosed with a calibrated syringe pump and independently verified with the scale. The other failure modes reported a risk reduction of 50% and on the whole the total PRI passes from 186 in case of the manual activity to 63 for the robotic one.

CONCLUSION
The FMECA analysis shows an overall reduction of the PRI over 66% with the robotic compounding with respect to the manual production. Automation not only decreases the occurrence of dangerous events thanks to the complete control of every single step of the compounding process, but also develops an error detection system through independent verification processes.

References:
Background and purpose

APOTECACommunity is a workgroup on robotics where all the users of APOTECAchemo can share their expertise. An annual meeting is organized to discuss with the manufacturer the next developments and define the best practice. The feedback collected during the meeting represents the base for the next system upgrade aimed at increasing performances.

Some improvements that we have suggested are included in the 2012-upgrade and affected our productivity: a new procedure for the reconstitutions; an extemporaneous picking list; a faster communication between the management software and the robot; a more efficient vision system for the vial label identification.

The aim of this work is to quantify the benefits that pharmacist reaped in the day-to-day work in terms of productivity (number of preparations/day), after the annual upgrade.

Material and Method

The APOTECAchemo performance was analysed before and after the 2012 upgrade. The influence of the most significant functionalities (an extemporaneous picking list, a new vision system and a dedicate procedure for the reconstitution of lyophilized drugs) on productivity was examined.

The change in the preparation time of lyophilized drugs with high stability [1] (Cyclophosphamide, Trastuzumab and Gemcitabine) was also investigated.

Results

An average of 45 preparations per day was compounded before the upgrade, with a maximum of 60 preparations. After the installation, an average of 83 preparations per day was recorded, with a maximum of 100.

The most affecting feature is the new procedure for the reconstitutions. Indeed the dissolution of stable lyophilized drugs (Cyclophosphamide, Trastuzumab and Gemcitabine) during “spare time” (weekend, early morning, lunch time) have allowed an average gain of 55 (11.5%), 72 (15%) and 24 (5%) minutes per day, respectively.

Conclusions

The new upgrade allowed an increase of 84.4% of the daily productivity. The constant multidisciplinary dialogue among the stakeholders (physicians, pharmacists, technicians and engineers) guarantees a better and better integration of APOTECAchemo in the daily clinical activity and a continuous development of the technology.
DISINFECTANT EFFICACY OF ULTRAVIOLET LIGHT IRRADIATION IN AN AUTOMATED SYSTEMS FOR THE ASEPTIC COMPOUNDING

BACKGROUND AND PURPOSE

Ultraviolet (UV) light irradiation is used in a variety of applications, such as food, air and water purification. The mechanism of UV disinfection differs considerably from chemical disinfectants: UV is mutagenic to bacteria, viruses and other microorganisms by damaging nucleic acids and preventing replication. However, the effectiveness of UV disinfection depends on a number of factors: time of UV exposure; power of the UV source; presence of UV barriers like airborne particles; microorganism resistance. This study was aimed at assessing the effectiveness of UV disinfection into APOTECAchemo, the robot for the compounding of antitumoral drugs in use at the University Hospital of Ancona. The Killing rate (KR) and the optimal time of exposure were determined.

MATERIAL AND METHOD

Five different microorganisms were chosen for the study in order to cover all the most common families of microbes:
- Candida albicans (fungus);
- Escherichia coli (Gram negative bacterium);
- Bacillus subtilis (sporing Gram positive bacterium);
- Staphylococcus aureus (Gram positive bacterium);
- Pseudomonas aeruginosa (Gram negative bacterium).

Different concentrations of each organism (from 10^7 CFU/ml to 0.5 CFU/ml) were subjected to UV radiation for different exposure times, using the robot’s UV equipment. The corresponding plates were located in two different positions inside the compounding room of APOTECAchemo in order to verify the influence of distance from UV source. After irradiation, the plates were incubated at 37°C for 24 hours and then the microbial load were evaluated.

The KR (logarithmic ratio between the concentration of microorganisms after and before irradiation) was plotted against the exposure time in order to graph the inactivation curves.

RESULTS

The UV radiation showed an unexpected high efficacy: a four-hour exposure recorded no microbial growth of all microorganisms at highest concentration.

Bacillus subtilis confirmed to be the strongest UV resistance microbe, indeed 4-hour exposure was necessary to kill 10^7 CFU/ml. The less resistant microorganism was Escherichia coli with 2-hour UV irradiation.

While after three-hours exposure, no colonies of S. aureus, C. albicans and Paeruginosa were observed.

The plates location inside the system showed only a slight influence on the killing rate, likely thanks to the mirror effect of the stainless steel surfaces.

CONCLUSION

The UV radiation is a fundamental step in the sanitization of workplaces. In fact, 4-hour exposure showed an effective sterilization (KR < 7) outcome, also in case of very resistant microorganisms (Bacillus subtilis). However, taking into consideration a reasonable risk of microbial contamination into a cleanroom (10^5 CFU/m² or 1 CFU/cm²), a day irradiation of 1 hour is sufficient to maintain the aseptic condition under ordinary condition.

References:
[1] UV lamp: peak emission 254 nm; irradiance@1m 22mW/cm², radiant flux 2.4W.