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Cytotoxic compounding robot

Particulate and microbiological cleanliness assessments in two European pharmacy aseptic units are discussed

Monsey McLeod¹

MPharm MSc

Bryony Dean

Franklin¹

BPharm MSc PhD

Peter Cowin²

BA Hons Chemistry

Ayo Ogunsanlu²

BSc Hons Microbiology MSc

Biotechnology

Alicia Tavella³

MPharm MSc

Carol Bastian³

MPharm MSc

Giusy Martelli⁴

MSc

Ann Jacklin^{1,5}

MPharm CHSM

¹Centre for Medication Safety and Service Quality, Imperial College Healthcare NHS Trust and The School of Pharmacy University of London, UK

²Quality Assurance Pharmacy Department Charing Cross Hospital Imperial College Healthcare NHSTrust UK

³Pharmacy Department Azienda Sanitaria dell'Alto Adige, Bolzano, Italy

⁴Health Robotics Bolzano, Italy

⁵Pharmacy Department Imperial College Healthcare NHS Trust, UK

Advances in diagnostics and cancer therapies over recent years have benefited many of our patients by helping them to live longer with improved quality of life. People are being diagnosed earlier and treatment initiated earlier, which often involves combination chemotherapy. For hospital pharmacy aseptic units, there is a challenge to meet this increased demand while maintaining a high quality service which is safe and efficient. One potential solution to this challenge is to utilise automated systems such as cytotoxic compounding robots (CCR) for the preparation of chemotherapy.

In 2007, the European Union (EU) approved funding for the market research and validation of one such CCR (CytoCare™, Health-Robotics, Bolzano, Italy) in a multi-national project, SafeChemo. More information on the SafeChemo project, which was completed in January 2009, can be found elsewhere.¹⁻³ Briefly, the SafeChemo consortium comprised four commercial partners working with three EU hospital sites, one each in the UK, Italy and Denmark. The project evaluated the CCR with respect to three main domains: safety, efficiency and human aspects. This article reports on two of the safety domain outcome measures: particulate concentration and microbiological cleanliness inside the CCR. These are key indicators of the safety of the internal CCR environment for the preparation of sterile medicinal products and are needed to confirm classification of an EU Good Manufacturing Practice (EU GMP) Grade A environment inside the CCR.^{4,5} Testing and validation (factory approval tests) of the CCR during the manufacturing process had already been performed prior to installing the CCR at each site and the findings presented here were determined post-installation in two EU hospital pharmacy aseptic units.

In addition, we also carried out experiments to explore the benefits of having three sets of detachable ultraviolet (UV) lights in the CCR on reducing surface microbiological burden prior to cleaning.

What is the importance?

There are routine tests and guidance for determining the suitability of conventional isolator technology for the preparation of sterile medicinal products. However, they have not been described for use in a complex robotic system such as a CCR.

The CCR studied is a robotic system which uses a combination of barcode technology and camera-captured image recognition to prepare sterile cytotoxic products under unidirectional airflow and negative pressure. It uses a triple-jointed robotic arm for performing compounding manipulations. None of these features are found in isolators or other conventional microbiological safety cabinets. The CCR therefore presents a potentially greater challenge for cleaning so testing its compliance with EU GMP guidance post-installation was considered to be essential.

Furthermore, although UV lights are known for their surface and aero-microbiological germicidal effect, they are not routinely used in clean air devices in many EU countries. Therefore, we also wanted to test the benefit of having UV lights in the CCR by exploring its ability to reduce microbiological burden (prior to any cleaning).

Method

This study took place in two hospital-based pharmacy aseptic units, one in the UK and one in Italy. Each unit provided a sterile manufacturing service typical of the country concerned, with approximately 15,000 parenteral cytotoxic doses produced per annum on each site. Data for this study were collected between December 2007 and December 2008 at the UK site and in December 2008 at the Italian site, post-installation but prior to commissioning each CCR to produce cytotoxic doses for patients.

The cytotoxic compounding robot

The CCR has an air-supply-filtration system (AIR) similar to that in other clean air devices such as microbiological safety cabinets, laminar air flow cabinets and aseptic isolators. There are three main chambers in the CCR: pre-load, carousel and working chambers (see Figure 1). These function as a materials transfer chamber, a materials store and a compounding chamber respectively. The pre-load chamber also has a barrier air flow system comprising a curtain of air flowing across the opening where materials are transferred which is comparable to that in a microbiological safety cabinet. Inside the CCR, UV lights are used (when the CCR is not in operation) on the highly reflective surfaces of the internal chambers and the robotic surfaces to help maintain microbiological cleanliness of these surfaces.

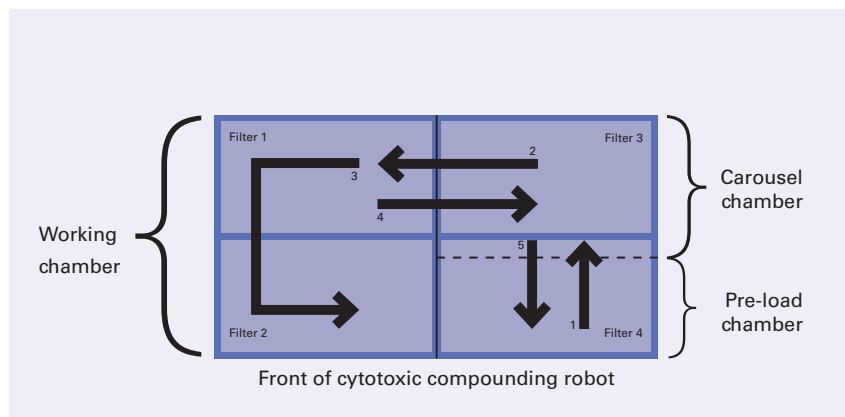


Figure 1. Cross-sectional representation of the three chambers within the cytotoxic compounding robot as viewed from above. The filters within each of the chambers are represented by shaded boxes and the dotted line represents an opening between the chambers where a sliding door is located. Numbered arrows illustrate the direction of flow of materials going into and out of the cytotoxic compounding robot in sequential order

There are UV lamps fixed into the ceiling of the carousel chamber as well as a set of removable UV lamps in each of the working and pre-load chambers. More details of the CCR can be found elsewhere.⁶

Particulate concentration and microbiological cleanliness

At each site, standard cleanroom cleaning was undertaken inside the CCR and the room where it was located prior to particulate and microbiological testing.⁷⁻⁹ To assess particulate concentration, a laser air particle counter was used to measure the concentration of airborne particles present in each of the three chambers of the CCR when the CCR was in operation. In addition, at the UK site, the particle counts were measured at a point nearest to cytotoxic filling and when the CCR was at rest. In accordance with local standard operating procedures, the measurements were repeated twice more at the UK site on different days and at the Italian site, three sets of measurements were taken in each of the three chambers. Particles of 0.5µm and 5.0µm sizes were recorded at the UK site, while the 0.3µm and 0.5µm sizes were recorded at the Italian site, both in accordance with local practice and ISO methods.⁷⁻⁹

Microbiological monitoring was performed using three standard techniques.⁷⁻⁹ Active air monitoring was performed using a microbiological air sampler located in the working and carousel chambers. One cubic metre of air was sampled and directed onto an agar plate containing tryptone soya agar (TSA) which was subsequently incubated at 30–35°C for seven days. The pre-load chamber was excluded as it had an opening to the cleanroom. Passive air monitoring was performed by exposing sets of two 90mm settle plates, one TSA and one sabouraud dextrose agar (SDA). Both the TSA and SDA plates were exposed for one hour at nine locations inside the CCR (one in the pre-load chamber, four in the carousel chamber and four in the working chamber). The TSA plates were incubated as above and the SDA plates at 20–25°C for seven days. Surface monitoring was performed using contact plates, for easily acces-

sible flat surfaces, and sterile swabs for uneven or hard to reach surfaces at a total of 34 locations inside the working chamber (10 contact plates, 24 swabs), 39 in the carousel chamber (13 contact plates, 26 swabs) and six in the pre-load chamber (six contact plates). Where swabs were used, they were transferred to TSA and SDA plates and incubated as before. At the UK site all microbiological monitoring was done three times in line with accepted UK practice

for assessing clean air devices.

At the Italian site, tests were performed once and no active air monitoring was performed, in line with local procedures. The same passive and surface microbiological tests were performed using the methods described for the UK site, however the number of locations differed slightly in accordance with advice received from the Italian hospital microbiology department who reviewed the testing. Passive air monitoring was performed in the working chamber only (four locations, same as the UK site). Surface monitoring was performed at a total of 22 locations inside the working chamber (10 contact plates, 12 swabs), six in the carousel chamber (six swabs) and six in the pre-load chamber (six swabs).

Testing effectiveness of UV lights on reducing microbiological burden

We conducted surface microbiological monitoring under three experimental conditions: first, with no use of UV lights (to measure the baseline microbiological burden inside the CCR); second, with the UV lights on the night before monitoring; and third, UV lights were used the night before and AIR was on during monitoring after the CCR and room had been cleaned (to represent usual working conditions). These experiments were carried out in the early period immediately post-installation, prior to the particulate and microbiological assessments described above and prior to any cleaning (except for the third experiment) as there was no commercial product available to provide a standard microbiological challenge. We used the mean number of colony-forming units (cfu) grown per plate within each chamber to compare the microbiological burden between different experimental conditions. Standard surface monitoring was performed using both contact plates and sterile swabs.

Results

Particulate concentrations and microbiological cleanliness

At both sites, all particle counts measured in each of the three chambers of the CCR were within the recom-

References

1. European Union. SafeChemo – ePrescription and Automation for a Safe Management of Cytostatics. Available online at: www.safechemo.eu/en/information/index.asp (Accessed 12 July 2009).
2. Jacklin AJ et al. *Eur J Hosp Pharm Prac* 2008;14:83–84.
3. Jacklin A. *Brit J Clin Pharm* 2009;1:39–40.
4. European Commission. (EudraLex), Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use. Annex I, Manufacture of Sterile Medicinal Products (corrected version, November 2008).
5. MHRA. Rules and Guidance for Pharmaceutical Manufacturers and Distributors (reprint 2007, first edition published 1971 as the Guide to Good Pharmaceutical Manufacturing Practice), Section II, Annex I, Manufacture of Sterile Medicinal Products, pages 86-89. London: Pharmaceutical Press; 2007.
6. Health Robotics. CytoCare™ robotic solution for the automated compounding of hazardous IVs. Available online at: www.healthrobotics.com/en/solutions/cyto-care/ (Accessed 12 July 2009).
7. British Standards Institution. BS EN ISO 14644–1:1999
8. British Standards Institution. BS EN ISO 14644–2:2000

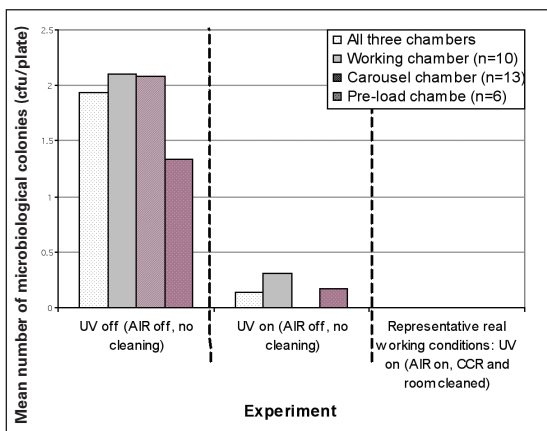


Figure 2. Surface monitoring using contact plates in the three chambers of the cytotoxic compounding robot under three experimental conditions (total number of contact plates in each experiment = 29)

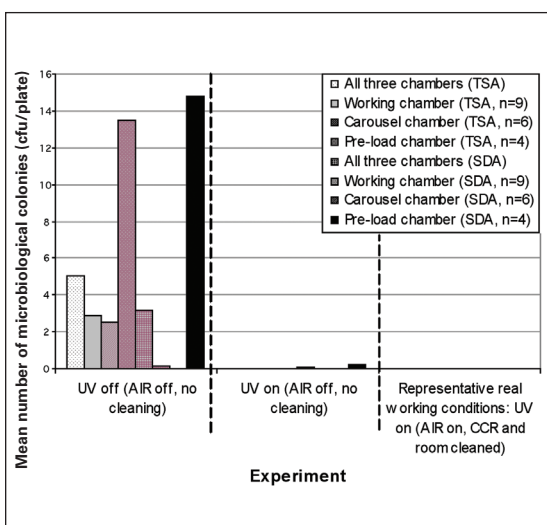


Figure 3. Surface monitoring using swabs in the three chambers of the cytotoxic compounding robot under three experimental conditions (total number of tryptone soya agar and sabouraud dextrose agar plates in each experiment = 19)

mended EU GMP Grade A limits. For the assessment of microbiological cleanliness, a total of 447 plates from 90 locations sampled were analysed at the UK site and a total of 62 plates from 38 locations at the Italian site. No microbiological colonies were cultured at either site.

Effectiveness of UV lights on reducing microbiological burden

Microbiological presence in the CCR prior to turning on the AIR or UV lights was confirmed (see Figures 2 and 3). The number of cfu observed per plate from surface monitoring using contact plates and swabs were less when UV lights had been on the night before than when they had been off.

EU GMP Grade A microbiological cleanliness specification for surfaces was achieved in each of the three chambers of the CCR when UV lights were used without AIR prior to any cleaning and after cleaning both the CCR and room. The latter experiment represented operating conditions and no microbiological colonies were cultured from any of the locations sampled.

Discussion

The use of CCRs offers a technological solution for pharmacy aseptic units faced with the challenges of meeting increasing demands while balancing operator safety and delivery of high quality products. In this study, we have described the methods we used to confirm that the CCR meets the EU GMP Grade A requirements post-installation in two EU hospital aseptic units. There were differences in the locations tested in the CCR which reflects the difference in practice between the two units. At the UK site, the aseptic unit is a licensed sterile manufacturing unit which is assessed by the Medicines and Healthcare Regulatory Agency and therefore more stringent testing of microbiological contamination was carried out by the unit. At the Italian site, the requirements were assessed as appropriate by the local hospital microbiological department. Both approaches demonstrated the compliance of EU GMP Grade A standards inside the

CCR post-installation, however continuous monitoring of the CCR and cleanroom are vital. In conjunction with other standard operational tests such as filter integrity and air flow velocity, both aseptic units have continued to monitor regularly the suitability of the environment inside the CCR (and aseptic unit) in accordance with the EU GMP using the methods described.

From the UV lights experiments, we were able to demonstrate that the use of UV lights the night before monitoring (even under 'dirty' conditions) can reduce the microbiological burden inside the CCR to within acceptable EU GMP Grade A classification limits. However, this should not be used as evidence that UV lights will reliably achieve EU GMP Grade A conditions inside the CCR without cleaning as we did not repeat our experiments and it was not performed under controlled conditions including the use of a standard microbiological challenge. Nonetheless, we believe our results support the use of UV lights inside the CCR as it lowers the microbiological burden prior to any cleaning, thereby providing us with greater assurance that the CCR satisfies the requirements for the production of sterile medicinal products. Consequently at the UK site, we were able to reduce the amount of regular cleaning and also reduce the downtime of the CCR (due to the monitoring and incubation times) from 10 days to one day post-maintenance work. This has reduced the time taken to clean the CCR (than if no UV lights had been used in the CCR), and also we believe the operator's exposure to potential traces of cytotoxic drugs have been reduced. To date, since the changes in cleaning and downtime were made at the UK site, microbiological cleanliness inside the CCR (and cleanroom) has been repeatedly monitored by the quality assurance department and EU GMP Grade A standards has been maintained.

Conclusion

This study has described how a CCR was assessed in two EU hospitals as achieving an EU GMP Grade A environment in the practice setting. In addition, our results demonstrate that the use of UV lights were effective in reducing the microbiological burden (as detected by surface microbiological monitoring) to levels within EU GMP Grade A limits even without manual cleaning. By using existing methods, we believe our approach would be a useful guide on how compliance can be assessed in similar systems elsewhere. ■

Acknowledgements

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- 9. International Standards Organization. ISO 14644-3 Cleanrooms and associated controlled environments – Part 3: Test methods.
- 10. Leonard D. *Hosp Pharm Eur* 2009; Available online at: www.pharmacyeurope.net/default.asp?title=AutomatingthePreparationofChemotherapyinUKPharmacyDepartment&page=article.display&article.id=18733 (Accessed May 2010).