The Hospital Pharmacy
The Capital Region of Denmark

MEDIA FILL TO VALIDATE THE ASEPTIC PREPARATION OF CYTOTOXICS ON AN AUTOMATED ROBOT

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Introduction
The Capital Region Pharmacy, Denmark has in 2013 installed and GMP qualified a semi-automated robot (APOTECAchemo) for cytotoxic compounding. A majority of the products produced on the robot will be stock held for more than 24 hours, which makes greater demands on the documentation of the aseptic process.

Objectives
To describe the performed initial performance qualification of the APOTECAchemo robot and personnel with media fill, the microbiological monitoring of the robot and the sorroundings and continuous particle monitoring.

Methods and study design
Media fill was carried out to simulate the compounding processes in order to evaluate sterility of the final products and to qualify the personnel.

Critical factors were taken into account in planning the simulations:
- all different compounding processes with liquid drugs, reconstitution of powder drugs were simulated
- all different types and sizes of final containers,
- high number of needle picks in the final containers
- personnel (number and time shift)

Table 1 Setup for performance of media fill on APOTECAchemo robot

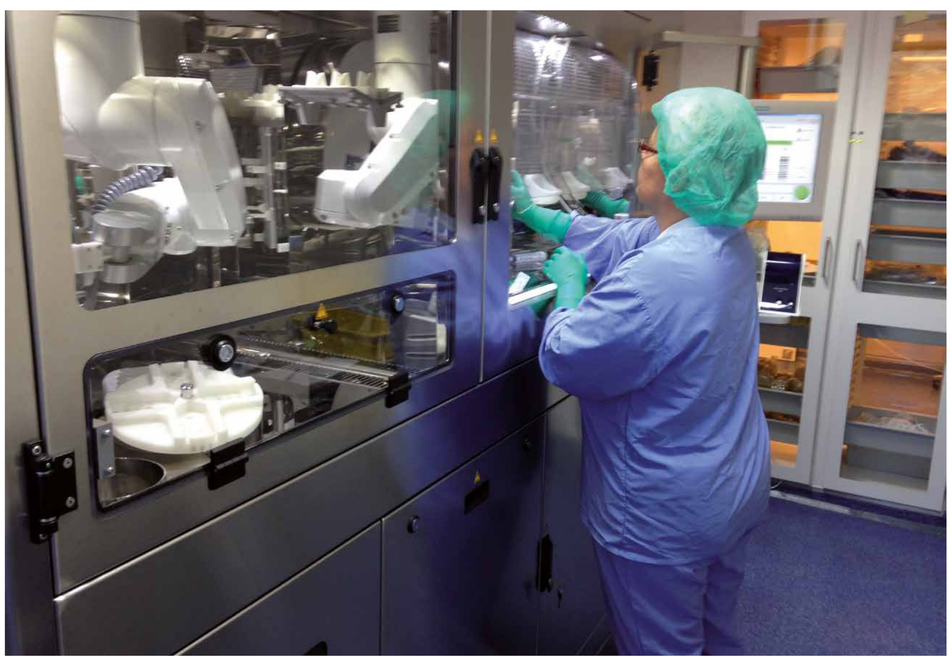
No.	Final container (ml)	Groth media - type and vol.		Reduce vol. of final container	Vol. in final container (ml)	Intervention no.
Simulation of patient specific compounding						
1	50	TSBx3	30	No	80	1
2	50	TSBx3	30	No	80	2
3	50	TSBx3	20	Yes	50	-
4	250	TSBx3	87,5	Yes	250	-
5	250	TSBx3	87,5	Yes	250	-
6	500	TSBx3	175	Yes	500	-
7	Infusor pump	TSBx3	100	N/A	256	-
8	100	TSBx1	50*	Yes	50	-
9	Infusor pump	TSBx1	50*	N/A	256	-
Simulation of batch production						
10	500	TSBx3	175	Yes	500	-
11	500	TSBx3	175	Yes	500	-
12	500	TSBx3	175	Yes	500	-
13	500	TSBx3	175	Yes	500	3
14	500	TSBx3	175	Yes	500	-
15	500	TSBx3	175	Yes	500	-
16	500	TSBx3	175	Yes	500	-
17	500	TSBx3	175	Yes	500	-
18	500	TSBx1	175	Yes	500	-

*Dedicated reconstitution made in the robot with TSBx1

Planned interventions were performed during the media fill to simulate “worst case” scenarios that could happen in a normal working day:

1. Open the door into the production zone and ”pick up” a vial (Simulation of a dropped vial)
2. Open the door into the production zone and ”clean” the bottom (Simulation of cleaning after a spill accident)
3. Empty the waste bin

Media fills were performed with tryptone soya broth (TSB), Ph. Eur. single (TSBx1) and tripple (TSBx3) strength. Documentation for test for sterility and growth promotion test were provided. It was taken into account that the dilution of the media did not exceed 1:3. Media fills were performed for at least eight hours a day, three days in a row. 108 final products (= 6 x Table 1) were produced and incubated for 14 days at 22,5 ± 2,5 °C.



Settle plates, contact plates were used in the three zones of the robot and in the surroundings to monitor microbiological contamination.

Particle counts in the production zone of the robot were monitored continuously during media fills.

225,4 mm

The acceptance criteria of the media fill were <1 contaminated unit and the acceptance criteria of the particle level was set in accordance with EN ISO 14644-2 and acceptance criteria of the microbiological monitoring was set according to EudraLex, Volume 4, Annex 1.

Results
After incubation, the units were inspected visually for microbial growth by QC. None of the products were contaminated and none of the particle counts taken during the media fill exceeded the acceptance criteria of grade A. The results of the microbiological monitoring showed that the production zone and carousel zone of the robot complied with the requirements for grade A ”in operation”. The loading zone which is adjacent to the grade C surroundings, complied with grade B ”in operation”.

Conclusions
With media fill and continuous particle monitoring, we assessed our technique, evaluated the aseptic preparation on the robot and qualified the operators. We also demonstrated that the environmental control is adequate to meet the requirements necessary to produce cytotoxic units for stock hold.

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No conflict of interest