CLEANING VALIDATION OF SOLUTION PRODUCTION IN A HOSPITAL PHARMACY

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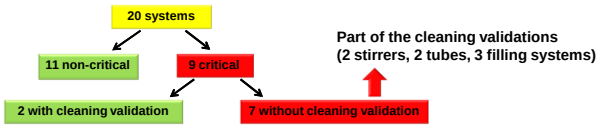
Objectives

Hospital pharmacies often have a limited amount of technical equipment to produce a large portfolio of pharmaceutical products. Therefore, multipurpose equipment is used for manufacturing of different pharmaceutical preparations, introducing the risk of transferring contaminants to secondary products. Cleaning of technical equipment should remove residues of products and cleaning agents, as well as avoid microbial contamination, to guarantee patient safety and high quality of subsequent products [1]. Therefore, effective cleaning procedures should be developed and validated for all process equipment wetted by the product. Subsequently, the risk of contamination for all possible production lines of liquid manufacturing could be assessed.

Methods

1. Evaluation of critical equipment/surfaces (multipurpose equipment with product contact)



2. Evaluation of the cleaning procedures
Use of residue-free cleaning agents (H_2O, EtOH)
→ no cleaning validation for the cleaning agents
→ no toxicological assessment for parenteral production necessary

3. Evaluation of the worst case active component
2 criteria: poorest water solubility (< 100 g/l) – physicochemical issue
→ worst case for aqueous cleaning agents (H_2O, EtOH)
lowest therapeutic dose – pharmacological issue
→ worst case for permitted limits
Target: One worst case active component enables an assessment of all production lines
→ evaluation of the whole available portfolio (32 products) ► Naphazoline nitrate

4. Analytical method validation of the worst case active component (HPLC)

5. Definition of the dirty hold time (24 hours)

6. Calculation of the analytical residue limits

$$1/1000\ \text{dose criteria} = \frac{\text{lowest therapeutic dose (previous dose)} \bullet \text{batch size (subsequent product)}}{1000 \bullet \text{maximum daily intake (subsequent product)}}$$

7. Calculation of the microbiological residue limits (from GMP-Guidelines)
≤ 25 **c**olony-**f**orming **u**nits / 25 cm² for cleanroom class C (sterile production)
≤ 50 CFU / 25 cm² for cleanroom class D (non-sterile production)

8. Execution of the analytical and microbiological cleaning validation

9. Analytical and microbiological assessment of the production lines
Evaluation of every possible production line (combination of stirrer, tank, tube and filling machine) with the largest wetted surface for each production division (sterile and non-sterile)
→ adding the single equipment residues and assessing the whole process (Fig. 1)

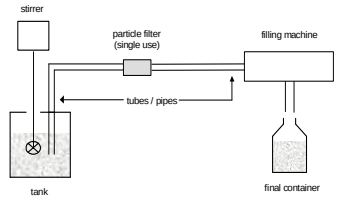
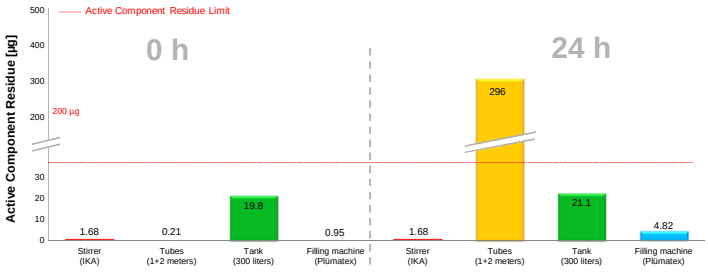


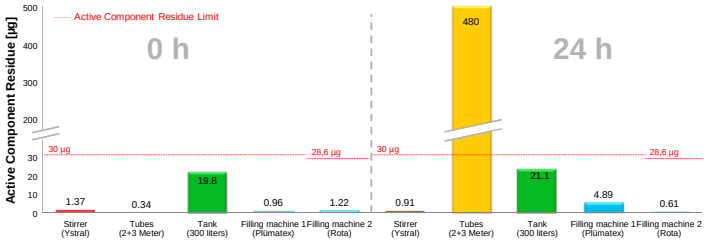
Figure 1: Schematic of the solution production process

Results

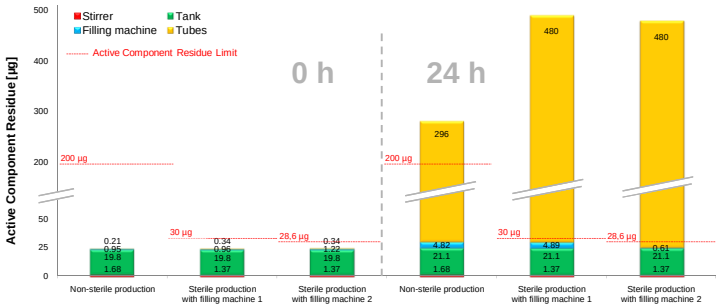
Equipment of non-sterile production: active component residue after cleaning



Equipment of sterile production: active component residue after cleaning



Additon of residues for the total solution production process



- The tubes (inner surface: **p**oly**t**etra**f**luoro**e**thylene) have to be cleaned immediately after the end of production (0 hours) in order to meet the residue limits. All other equipment (critical surface: stainless steel) met their residue limits even after a dirty holding time of 24 hours.
- The whole solution production process fulfilled the residue limits, with consideration of the cleaning time restriction of the tubes.
- No colony-forming units (0 CFU) were found on the completely dried sampled surface of the equipment after cleaning. The microbiological residue limits were met by the equipment in both cleanroom classes (C: equipment for sterile production, D: equipment for non-sterile production).

Discussion and Conclusions

- Residues of the active component may adhere to the inner surface of the tubes (PTFE). These residues are very difficult to remove by cleaning.
- After 24 hours, residues of the active component were dried, whereby removal of lipophilic active components with hydrophilic agents is more complicated.
- Turbulent flows and the rinsing of cavities from both directions could achieve a better cleaning outcome.
- A dried surface, consisting of stainless steel or PTFE, can reach the same microbiological results as an identical autoclaved material.
- **PDE value:** The maximum acceptable active component residue is referenced to the PDE value (**p**ermitted **d**aily **e**xposure), which reflects an accepted daily exposure of constant magnitude over a lifetime [1]. Patients' stays in hospitals are usually short or medium term. Therefore the use of the PDE value as the acceptable limit of active component residue for production in hospital pharmacies is limited. The evaluation of the residue limits with PDE value should be conducted as a risk assessment, considering batch size, maximum daily dose and duration of therapy.

Acknowledgement

We would like to thank all members of the production, quality control and quality assurance units of the Hospital Pharmacy of the University Hospital Basel.

Literature:
[1] European Commission. Annex 15: Qualification and Validation. In: EU Guidelines for Good Manufacturing Practice for Medical Products for Human and Veterinary Use. 4th ed. Brussels: European Commission; 2015. p. 1–16

Presentation:
23rd EAHP Congress
21-23 March 2018, Gothenburg (Sweden)

3PC-037

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