Cleaning validation of cleanrooms and preparation equipments

Pharmacie

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Useful Definitions

- Cleaning :
  - Removal of soil particles /product residues from surfaces by the use of chemical agents and manual or mechanical action
- Sanitization (Disinfection) :
  - Destruction of vegetative state organisms

Legal Basis

- "Particular attention should be accorded to the validation of … cleaning procedures" (WHO)
- "Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure" (PIC/S, EU GMP)
- "The data should support a conclusion that residues have been reduced to an 'acceptable' level" (FDA)

New in Hospital Pharmacy

- Development of the sterile drugs prepared by aseptic techniques
- Centralization of the preparation of cytotoxic drugs in hospital pharmacies

Problems

- Cross-contamination of the preparations
- Microbiological problems due to poor cleaning
- Chemical contamination of the operators

Cross-contamination of the preparations

- Hospital Pharmacy Production units :

  a Multi-product facility

  - an effort of validating the cleaning of each piece of equipment which has been exposed to a product
  - if not, considering seriously the possibility and the cost of permanently dedicating this equipment to a single product

Cross-contamination of the preparations

- Hospital Pharmacy Production units :

  a Multi-product facility

  - For each Equipment :
    - cleaning validation is performed during process development
    - Test-until-clean not considered acceptable
  - The validation methodology :
    - Products which simulate the physicochemical properties of the substance to be removed may be considered for use instead of the substances themselves, when such substances are either toxic or hazardous

Microbiological aspects

- There should be some documented evidence that routine cleaning and storage of equipment do not allow microbial proliferation : equipment should be dried before storage
- The control of the bioburden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility

Operators Chemical contamination

- Preparation of cytotoxic drugs and other hazardous drugs
  - Contamination due to aerosol formation and drugs sublimation/evaporation
  - Spill management
  - After production cleaning procedures and the risk assessment

Operators Chemical contamination

- The risk associated with occupational low-level exposure has not been determined
- Without evidence to the contrary, risk is assumed to be present and proportional to exposure in a dose-dependent fashion
- A GMP compliant Cleaning validation covers also operators risks

Defining the problem

- **Product (patient) oriented**
  - **Cross contamination**
  - **Residues**
  - **Microbiology**
- Operator oriented
  - Contamination risk
  - Accumulation problem due to poor cleaning

Ideal cleaning solution

- Non-toxic to operators
- Non-flammable
- Fast-drying but not reasonably so
- Not harmful to clean room surfaces
- Not likely to leave particles or residue that could be harmful to the product
- Effective in removing undesirable contamination
- Reasonably priced

Possible contaminants

- Product residues
- Cleaning agent residues and breakdown
- Airborne matter
- Lubricants, ancillary material
- Decomposition residues
- Bacteria, mould and pyrogens

Strategy on cleaning validation

- Product contact surfaces
- After product changeover
- Bracketing products for cleaning validation
- Periodic re-evaluation and revalidation

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Cleaning Validation Protocol I

- Objective of the validation
- Responsibility for performing and approving validation study
- Description of equipment to be used
- Interval between end of production and cleaning, and commencement of cleaning procedure

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Cleaning Validation Protocol II

- Cleaning procedures to be used
- Any routine monitoring equipment used
- Number of cleaning cycles performed consecutively
- Sampling procedures used and rationale
- Sampling locations (clearly defined)

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Record of Cleaning Validation

- Analytical methods including Limit of Detection (LOD) and Limit of Quantification (LOQ)
- Acceptance criteria and rationale
- When revalidation will be required
- Must have management and QA involvement

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Results and reports

- Cleaning record signed by operator, checked by production and reviewed by QA
- Final Validation Reports, including conclusions

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Personnel

- Manual cleaning methods are difficult to validate
- Must have good training
- Must have effective supervision
- Cannot validate people; can measure proficiency

Microbiological aspects

- Include in validation strategy
- Analyze risks of contamination
- Consider equipment storage time
- Equipment should be stored dry
- Sterilization and pyrogen contamination

How to sample

- Swab/swatch
- Rinse fluid
- Placebo
- The sample transport and storage conditions should be defined

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Swab samples

- Direct sampling method
- Reproducibility
- Extraction efficiency
- Document swab locations
- Disadvantages
  - inability to access some areas
  - assumes uniformity of contamination surface
  - must extrapolate sample area to whole surface

Rinse samples

- Indirect method
- Combine with swabs
- Useful for cleaning agent residues
- pH, conductivity, TOC
- Insufficient evidence of cleaning
- Sample very large surface areas
- Need specific and sensitive analytical method

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Analytical methods I

- Validate analytical method
- Must be sensitive assay procedure:
  - HPLC, GC, HPTLC
  - TOC
  - pH
  - conductivity
  - UV
  - ELISA

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Analytical methods II

Check:

- Precision, linearity, selectivity
- Limit of Detection (LOD)
- Limit of Quantification (LOQ)
- Recovery, by spiking
- Consistency of recovery

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Setting limits I

- Regulatory authorities do not set limits for specific products
- Logically based
- Limits must be practical, achievable and verifiable
- Allergenic and potent substances
- Limit setting approach needed

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Setting limits II

- Uniform distribution of contaminants not guaranteed
- Decomposition products to be checked
- Setting limits; cleaning criteria:
  - visually clean
  - 10 ppm in another product
  - 0.1% of therapeutic dose

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Setting limits: "Visually clean"

- Always first criteria
- Can be very sensitive but needs verification
- Use between same product batches of same formulation
- Illuminate surface
- Spiking studies

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Setting limits: “10 ppm”

- Historical
- In some poisons regulations
- Pharmacopoeias limit test
- Assumes residue to be harmful as heavy metal
- Useful for materials for which no available toxicological data
- Not for pharmacologically potent material

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Setting limits: not more than 0.1%

- Proportion of MINIMUM daily dose of current product carried over into MAXIMUM daily dose of subsequent product
- Need to identify worst case

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Auto-inspection questions

- How is equipment cleaned?
- Are different cleaning processes required?
- How many times is a cleaning process repeated before acceptable results are obtained?
- What is most appropriate solvent or detergent?
- At what point does system become clean?
- What does visually clean mean?
- When prefer to use disposable devices?

Operator Validation

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Operator Validation

Validation Elements

- Validation of each operator evaluating his capacity to control chemical contaminations during cytotoxic preparations
- Scheduled at the end of the work session with a second controlling operator
- A total validation time of 60 minutes
- “Worst Conditions” Concept
- Negative pressure isolator
- A total cleaning of the isolator after the validation

R. Ing & al., GSASA Congress Zurich, 2005,

Operator Validation

Validation Materials

- A non-toxic tracer : 0,1 M Quinine HCl solution
- KCl 1 M 50 mL vials
- NaCl 0.9% solution infusion bags
- Sterile : Cytosafes, syringes, needles, stoppers, Transfer-set, tubing, connectors, gloves, working pad, waste bag, …

R. Ing & al., GSASA Congress Zurich, 2005,

Operator Validation

Validation Procedure

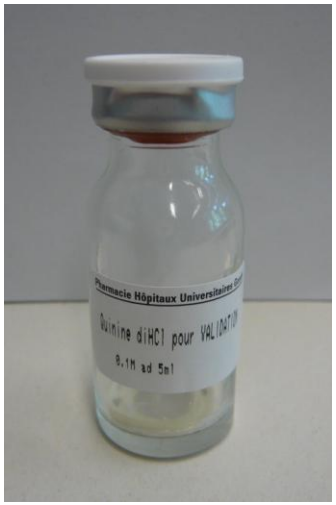
- Sterile gloves over the isolator gloves
- Dissolve the quinine vials with the solvent to have a final 0.1 M solution (drug reconstitution simulation)
- Preparation of 4 different drug simulation

R. Ing & al., GSASA Congress Zurich, 2005,

Operator Validation

Validation Procedure

20
x



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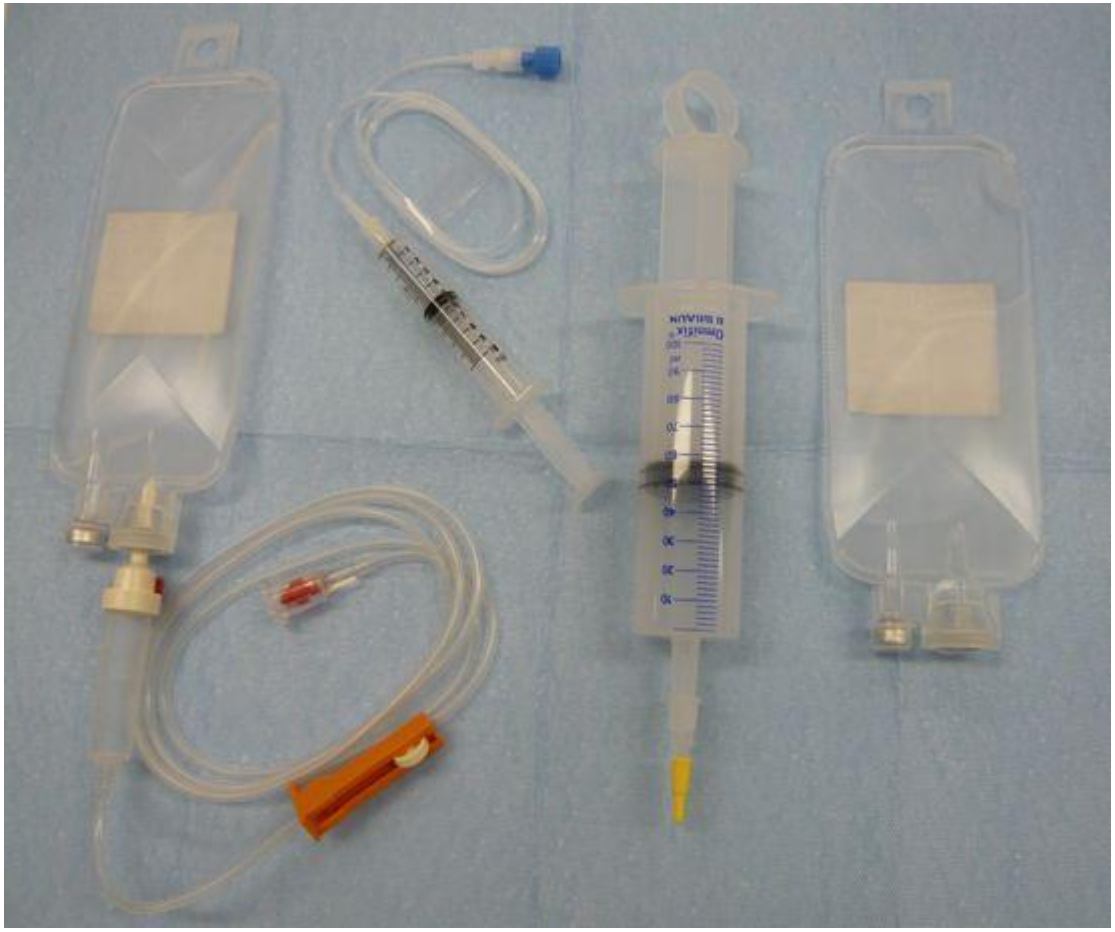

R. Ing & al., GSASA Congress Zurich, 2005,

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Operator Validation

Detection equipment

- Fluorimetric detection
  (Perkin Elmer LS 40)

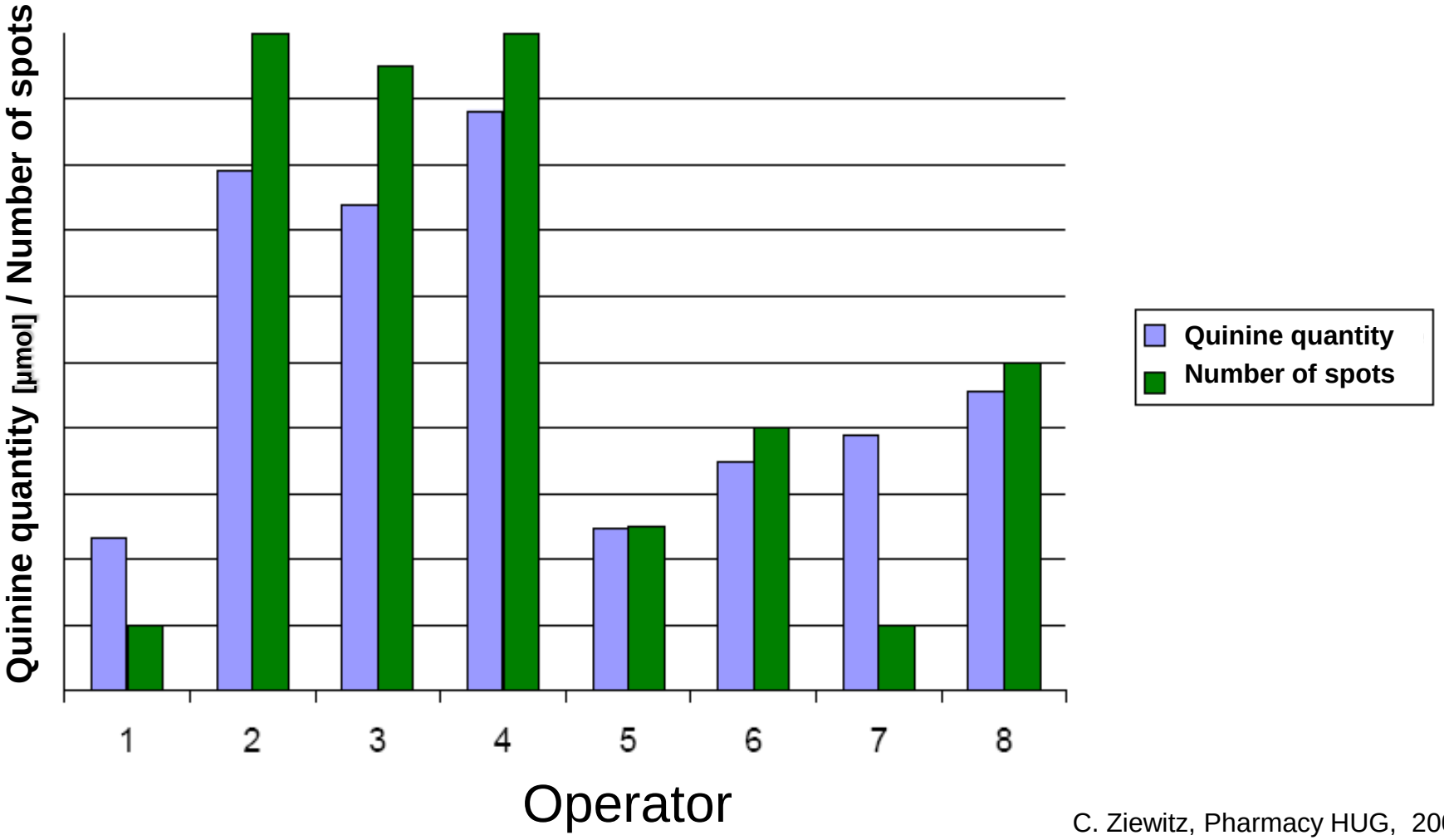
- UV light
  (CAMAG)

  Working pad

R. Ing & al., GSASA Congress Zurich, 2005,

Operator Validation

Results



C. Ziewitz, Pharmacy HUG, 2008

Operator Validation

Discussion

- Detected quantities:
  - **0.116 – 0.441 µmol** of Quinine
  - **(= 1.16 – 4.41 µl of the Quinine 0.1M solution)**
- « Acceptable level » according to FDA:
  - **0.1%** of the daily dose of the active ingredient

  - **5-FU 50 mg/ml, Daily dose 1000 mg**
    - « acceptable level » →1000 µg
    - Detected quantity equivalence : min → 58 µg
      max → 220 µg
  - **Vincristine 1 mg/ml, Daily dose 2 mg**
    - « acceptable level » → 2.0 µg
    - Detected quantity equivalence : min → 1.1 µg
      max → 4.4 µg

C. Ziewitz, Pharmacy HUG, 2008

General Conclusions

- Need for a cleaning validation strategy
- Assess each situation on its merits
- Scientific rationale must be developed
  - equipment selection
  - contamination distribution
  - significance of the contaminant and the contamination level
- "Visually clean" may be all that is required
- Disposable devices each time it is possible
- Developing non-toxic evaluation methods

References

- Supplementary Training Modules on Good Manufacturing Practices, WHO, EDM , 01.2002
- FDA. "Guide to Inspectors of Validation of Cleaning Procedures," 1993
- Health Canada, Health Products and Food Branch Inspectorate, "Good Manufacturing Practices - Cleaning Validation Guidelines, 2000

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Thank You