Supplementary Training Modules on Good Manufacturing Practices

CLEANING VALIDATION

Dr.D.VARUN

Professor & Academic Director

SRI INDU INSTITUTE OF PHARMACY

Hyderabad

Validation

Objectives

To review:

- General requirements
- Validation protocol requirements
- How to check limits
- Analytical requirements
- Sample methods

Validation

Why cleaning validation is so important (1)

- Pharmaceuticals can be contaminated by potentially dangerous substances
- Essential to establish adequate cleaning procedures

Validation

Why cleaning validation is so important (2)

- "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)
- "The data should support a conclusion that residues have been reduced to an 'acceptable' level" (FDA)

Validation

Possible contaminants

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

Validation

Strategy on cleaning validation

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

Validation

Cleaning validation protocol (1)

Should include :

- Objective of the validation
- Responsibility for performing and approving validation study
- Description of equipment to be used

Validation

Cleaning validation protocol (2)

Should include:

- Interval between end of production and cleaning, and commencement of cleaning procedure
- 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)

Validation

Record of cleaning validation

Should include :

- Data on recovery studies
- Analytical methods including Limit of Detection and Limit of Quantitation
- Acceptance criteria and rationale
- When revalidation will be required
- Must have management and QA involvement
- Management commitment and QA involvement

Validation

Results and reports

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

Validation

Personnel

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

Validation

Microbiological aspects

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

Validation

How to sample

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

Validation

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*

Validation

Rinse samples

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

Validation

Analytical method (1)

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

Validation

Analytical method (2)

Check:

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

Validation

Setting limits (1)

- 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

Validation

Setting limits (2)

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

Validation

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

Validation

Setting limits: "10ppm"

- 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

Validation

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

Validation

Other issues

- Clean-In-Place (CIP) systems
- Placebo studies
- Detergent residues; composition should be known
- Scrubbing by hand

Validation

Questions for the GMP Inspector to ask

- 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?

Validation

Conclusion

- The manufacturer needs a cleaning validation strategy
- Assess each situation on its merits
- Scientific rationale must be developed
  - *equipment selection*
  - *contamination distribution*
  - *significance of the contaminant*
- "Visually clean" may be all that is required