



Connecting People, Science and Regulation®



ICH Q7 Chapter 5 & 12.7: Process Equipment & Cleaning Validation



PDA - PIC/S ICH Q7 Training

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Content

- **Design & Construction (5.1)**
- **Equipment Maintenance and Cleaning (5.2)**
- **Cleaning Validation (12.7)**
- **Calibration (5.3)**
- **Computerised Systems (5.4)**



5.1 Equipment Design / Construction

- **Equipment used in the manufacture of intermediates and APIs should be (5.10)**
 - Of appropriate design and adequate size
 - Suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance
 - Constructed so that contact surfaces do not alter quality of intermediates and APIs beyond official or established specifications

5.1 Equipment Design / Construction

- Major equipment and permanently installed processing lines should be **appropriately identified** (5.13)
 - ◆ *There should be a clear identifier to trace equipment used and which product is running at which train (ID number)*
 - ◆ *Permanent processing lines (piping) should be identified with the content and the direction of flow*
 - ◆ *Often it had been shown beneficial to also label flexible transfer lines*



5.1 Equipment Design / Construction

- **Lubricants, heating fluids or coolants should not contact intermediates or APIs so as to alter their quality beyond the official or established specifications (5.14)**
 - ◆ *This should be achieved via equipment design and maintenance activities*
- **Wherever possible, food grade lubricants and oils should be used (5.14)**
 - ◆ *Ensure clear verification / certification of the ‘food grade’*



5.1 Equipment Design / Construction

- **Closed or contained equipment should be used, whenever appropriate**
(5.15)

◆ *Avoid contaminations*



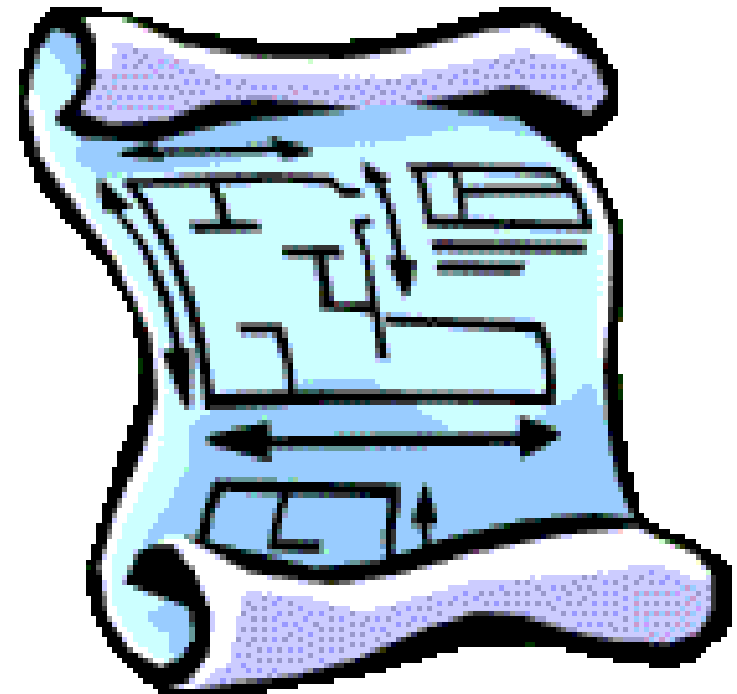
5.1 Equipment Design / Construction

- Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize risk of contamination (5.15)



5.1 Equipment Design / Construction

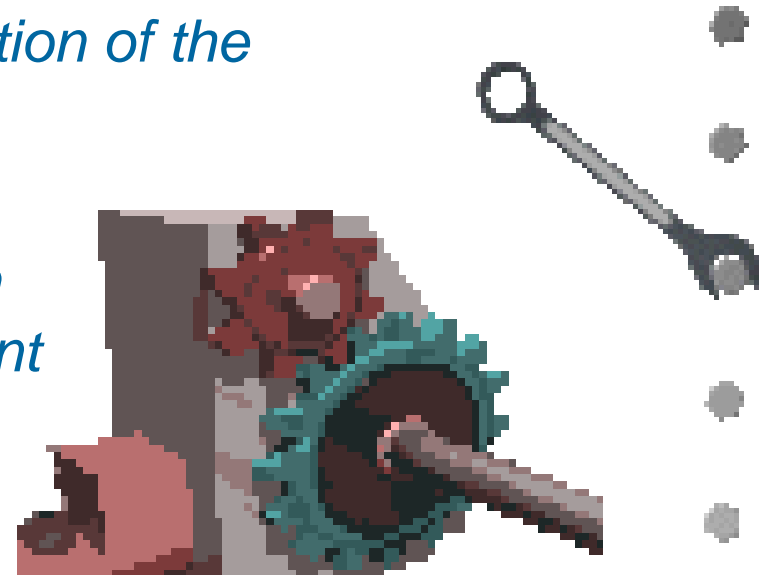
- **A set of current drawings for equipment and critical installations should be maintained (5.16)**
 - ◆ *Have drawings of the facility design (,as built‘) at all times updated*
 - ◆ *Examples for benefit:*
 - *Cleaning: recognise critical areas*
 - *Maintenance*



5.2 Equipment Maintenance/Cleaning

- **Preventive maintenance** schedules and procedures should be established (5.20)

- ◆ *Have a plan and a proven execution of the previous one*
- ◆ *Be able to keep up to date*
- ◆ *Poor maintenance could result in e.g. contamination risk, equipment failures, mal function*
- ◆ *Keep the equipment in an adequate state of operation*



5.2 Equipment Maintenance/Cleaning

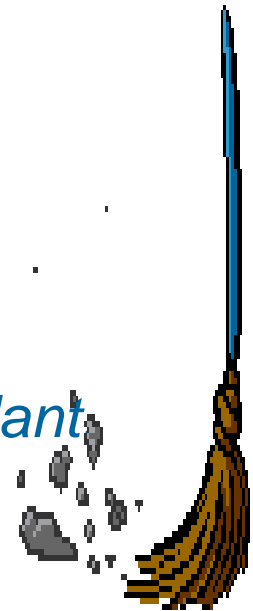
- **Written procedures for cleaning equipment should include (5.21)**

- Assignment of responsibility
- Cleaning schedules, including, where appropriate, sanitizing schedules
- Complete description of methods and materials

- ◆ *The written instructions should be based on a clear understanding of the design and construction of the plant*

- ◆ *Hard to clean areas of equipment should be identified for disassembling, cleaning and verification*

- ◆ *Product characteristics should be taken into account*



5.2 Equipment Maintenance/Cleaning

- **Written procedures for cleaning equipment should include (continued) (5.21)**
 - Removal or obliteration of previous batch identification
 - Inspection for cleanliness immediately before use, if practical
 - Maximum time that may elapse between completion of processing and equipment cleaning, when appropriate
- ◆ *In case of manual operation set clear requirements in the procedures to allow consistent application of the cleaning methods*
- ◆ *Dirty hold times / Clean hold times should be considered (see cleaning validation)*



5.2 Equipment Maintenance/Cleaning

- **Equipment and utensils should be cleaned, stored, and where necessary, sanitized, to prevent contamination or carry-over of materials (5.22)**
 - Equipment assigned to continuous production or campaign production should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (5.23)
 - Non-dedicated equipment should be cleaned between production of different materials to prevent cross - contamination (5.24)

5.2 Equipment Maintenance/Cleaning

- **Acceptance criteria for residues, choice of cleaning procedures and cleaning agents should be defined and justified (5.25)**
- **Equipment should be identified as to its contents and its cleanliness status by appropriate means (5.26)**



- ◆ *If 'clean in place' systems are used there should be appropriate controls that the system is functioning correctly for its intended purpose (e.g. flow and pressure of cleaning agents and orientation and function of spray balls)*



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ICH Q7 Chapter 12.7: Cleaning Validation



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12.7 Cleaning Validation

- **Cleaning procedures should normally be validated**
(12.70)
 - ◆ *For complex API plants validating cleaning processes might not be possible to the extent that there is absolute confidence in the cleaning method without performing verification at each change over.*
- **Cleaning validation should be directed to situations or process steps where contamination or carryover of materials pose the greatest risk to API quality**
(12.70)
 - ◆ *For all changeovers cleaning according to appropriate standards should be conducted.*

12.7 Cleaning Validation

- **If residues are removed by subsequent purification steps, it may be unnecessary to validate equipment cleaning procedures in early production steps (12.70)**
 - ◆ *Cleaning need to be performed and verified to appropriate standards*
 - ◆ *Evidence is needed that residues will be removed by the process to a level they typically found at end of cleaning*
 - ◆ *Other example might be*
 - *Two consecutive steps of the same syntheses*
 - *Dedicated versus multi purpose equipment*



12.7 Cleaning Validation

- **Validation of cleaning procedures should reflect actual equipment usage patterns (12.71)**
- **If various APIs or intermediates are manufactured in the same equipment and equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation (12.71)**

12.7 Cleaning Validation

- **Selection of intermediate or API for cleaning validation should be based on (12.71)**
 - Solubility
 - Difficulty of cleaning
 - Calculation of residue limits based on potency, toxicity, and stability
 - Description of equipment to be cleaned
 - ◆ *Same equipment configuration for all relevant molecules*
 - ◆ *The justification for the molecule selected should be recorded in the cleaning validation documents (e.g. master plan)*

12.7 Cleaning Validation

- **Cleaning validation protocol should include (12.72)**
 - Description of equipment to be cleaned
 - Procedures
 - Materials
 - Acceptable cleaning levels
 - Parameters to be monitored and controlled
 - Analytical methods
 - Types of samples to be obtained, collection and labeling procedures

◆ *Explain the extended testing during cleaning validations*

12.7 Cleaning Validation

- **Sampling should include swabbing, rinsing, or alternative methods, as appropriate, to detect both insoluble and soluble residues (12.73)**
- **Sampling methods should be capable of quantitatively measuring levels of residues on equipment surfaces after cleaning (12.73)**
- **Swab sampling may be impractical when contact surfaces are not easily accessible due to equipment design and/or process limitations (12.73)**
 - ◆ *The plant need to be designed as far as possible to allow swabbing even on a limited access bases*

12.7 Cleaning Validation

- **Analytical methods should be validated and sufficiently sensitive to detect established acceptable levels of residues or contaminants (12.74)**
- **Residue limits should be practical, achievable, verifiable (12.74)**
 - ◆ *If required residue limits are unachievable then there may be a need for dedicated equipment or manage the change overs from the product portfolio*
- **Limits can be established based on 'lowest' known pharmacological, toxicological, or physiological activity of the API or its most deleterious component (12.74)**

12.7 Cleaning Validation

- **Equipment cleaning/sanitation studies should address microbiological and endotoxin contamination for those processes where (12.75)**
 - There is a need to reduce total microbiological counts or endotoxins in the API
 - Where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products)
- ◆ *The microbiological monitoring during biotech up stream processing has the purpose to protect the organism making the API*

12.7 Cleaning Validation

- **Cleaning procedures should be monitored at appropriate intervals after validation to ensure these are effective when used during routine production (12.76)**
- **Equipment cleanliness can be monitored by (12.76)**
 - Analytical testing
 - Visual examination, where feasible
- ◆ *Visual examination may require use of endoscope or splitting equipment it should be done as much as possible*
- ◆ *Failure of cleaning (including manual cleaning) should be recorded through a deviation system and available as input to validation review*

5.3 Equipment Calibration



- **Control, weighing, measuring, monitoring and testing equipment critical for ensuring quality of intermediates or APIs should be calibrated as per written procedures and established schedules (5.30)**
- ◆ *When equipment is calibrated should be initially recorded ‘as found’ and ‘as left’*
- ◆ *Calibration should cover the full operating range of the equipment*
- ◆ *Schedules should be established to a known reliability and stability of the equipment*

5.3 Equipment Calibration

- **Calibrations should be performed using standards traceable to certified standards, if they exist (5.31)**
 - ◆ *If they do not exist appropriate scientifically justifiable approach should be taken*
- **Calibration status of critical equipment should be known and verifiable (5.33)**



5.3 Equipment Calibration

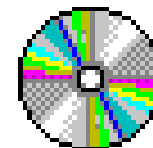
- **Deviations in calibrations involving critical instruments should be investigated to determine impact on quality of intermediates or APIs manufactured using the equipment since the last successful calibration (5.35)**



- ◆ *As a minimum critical instruments are those that measure critical parameters*

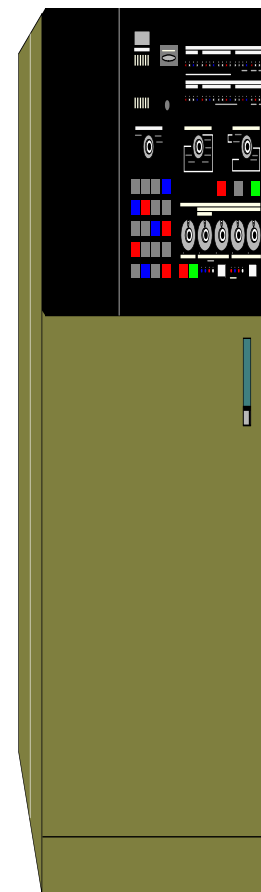
5.4 Computerised Systems

- **GMP related computerized systems should be validated (5.40)**



5.4 Computerised Systems

- **Depth and scope of validation depends on diversity, complexity, and criticality of computerized application (5.40)**
 - ◆ *The validation requirements should be established by people with a very clear and detailed understanding of the systems and impact on GMP controls*
- **Appropriate installation and operational qualification should be conducted to demonstrate suitability of computer hardware and software (5.41)**



5.4 Computerised Systems

- **If critical data is entered manually, the accuracy of the entry should be checked, either by a second operator or the system itself (5.45)**
- **Data can be recorded by a second means in addition to the computer system (5.49)**



5.4 Computerised Systems

- **Control to prevent unauthorised access or changes to data (5.43)**
 - ◆ *Pay special attention on the access to recipes*
- **Procedures for maintenance (5.44)**
- **Incidents should be recorded and investigated (5.46)**
- **Back-up system should be provided (5.48)**
 - ◆ *Make sure that the back up's do not get overwritten*

Key Messages

- **Appropriate design and maintenance of equipment**
 - Designed to avoid contamination and cross-contamination
 - Impact on GMP controls of computerised systems should be understood and validated
 - Calibration schedules and procedures should be justified on a science based approach
- **Cleaning should be managed as the process**
 - Failures should be recorded and investigated
 - Effectiveness to be monitored



ICH Q7 QaA *Clarification of Uncertainties*

1. For dedicated equipment, is 'visually clean' acceptable for verification of cleaning effectiveness, (i.e., no expectation for specific analytical determination)?
2. Should acceptance criteria for residues be defined for dedicated equipment?
3. Is it expected that equipment cleaning time limits be confirmed in cleaning validation?
4. Is it expected that campaign manufacturing be addressed in cleaning validation?
5. At product changeover, are both visual examination and analytical testing necessary to verify that equipment is clean?

ICH Q7 Q&A, 2015

