MANUFACTURING & QUALITY AUDIT DIVISION
CENTRE FOR DRUG ADMINISTRATION

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GUIDANCE NOTES ON CLEANING VALIDATION

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GUIDANCE NOTES

Subject: CLEANING VALIDATION

1.0 Principle

1.1 Pharmaceutical products and active pharmaceutical ingredients (APIs) can be contaminated by other pharmaceutical products or APIs, by cleaning agents, by micro-organisms or by other material (e.g. air-borne particles, dust, lubricants, raw materials, intermediates, auxiliaries). In many cases, the same equipment may be used for processing different products. To avoid contamination of the following pharmaceutical product, adequate cleaning procedures are essential.

1.2 Cleaning procedures must strictly follow carefully established and validated methods of execution. This applies equally to the manufacture of pharmaceutical products and active pharmaceutical ingredients (APIs). In any case, manufacturing processes have to be designed and carried out in a way that contamination is reduced to an acceptable level.

1.3 Cleaning Validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing of pharmaceutical products or active pharmaceutical ingredients (APIs).

1.4 Objective of the Cleaning Validation is the confirmation of a reliable cleaning procedure so that the analytical monitoring may be omitted or reduced to a minimum in the routine phase.

2.0 Purpose and Scope

2.1 These guidance notes describe the validation of cleaning procedures for the removal of contaminants associated with the previous products, residues of cleaning agents as well as the control of potential microbial contaminants.

2.2 These guidance notes apply to the manufacture of pharmaceutical products (final dosage forms) and of active pharmaceutical ingredients (APIs).

3.0 General

3.1 Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts into which product may migrate. For example, seals, flanges, mixing shaft, fans of ovens, heating elements etc.

3.2 Cleaning procedures for product changeover in the case of marketed products should be fully validated.

3.3 Generally in case of batch-to-batch production it is not necessary to clean after each batch. However, cleaning intervals and methods should be determined.

3.4 Several questions should be addressed when evaluating the cleaning process. For example:

- At what point does a piece of equipment or system become clean?
- What does visually clean mean?
- Does the equipment need to be scrubbed by hand?
- What is accomplished by hand scrubbing rather than just a solvent wash?
- How variable are manual cleaning processes from batch to batch and product to product?
- What is the most appropriate solvent or detergent?
- Are different cleaning processes required for different products in contact with a piece of equipment?
- How many times need a cleaning process be applied to ensure adequate cleaning of each piece of equipment?

3.5 Cleaning procedures for products and processes which are very similar, do not need to be individually validated. It is considered acceptable to select a representative range of similar products and processes concerned and to justify a validation programme which addresses the critical issues relating to the selected products and processes. A single validation study under consideration of the "worst

case" can then be carried out which takes account of the relevant criteria. This practice is termed "Bracketing".

3.6 At least three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.

3.7 Raw materials sourced from different suppliers may have different physical properties and impurity profiles. Such differences should be considered when designing cleaning procedures, as the materials may behave differently.

3.8 Control of change to validated cleaning procedures is required. Re-validation should be considered under the following circumstances:

3.8.1 Re-validation in cases of changes to equipment, products or processes,

3.8.2 Periodic re-validation at defined intervals.

3.9 Manual methods should be reassessed at more frequent intervals than clean-in-place (CIP) systems.

3.10 It is usually not considered acceptable to "test until clean". This concept involves cleaning, sampling and testing, with repetition of this sequence until an acceptable residue limit is attained. For the system or equipment with a validated cleaning process, this practice of "test until clean" should not be required. The practice of "test until clean" is not considered to replace the need to validate cleaning procedures.

3.11 Products which simulate the physicochemical properties of the substance to be removed may be used instead of the substances themselves, where such substances are either toxic or hazardous.

4.0 Documentation

4.1 A Cleaning Validation Protocol is required laying down the procedure on how the cleaning process will be validated. It should include the following:

- The objective of the validation process,

- Responsibilities for performing and approving the validation study,
- Description of the equipment to be used,
- The interval between the end of production and the beginning of the cleaning procedures,
- Cleaning procedures to be used for each product, each manufacturing system or each piece of equipment,
- The number of cleaning cycles to be performed consecutively,
- Any routine monitoring requirement,
- Sampling procedures, including the rationale for why a certain sampling method is used,
- Clearly defined sampling locations,
- Data on recovery studies where appropriate,
- Analytical methods including the limit of detection and the limit of quantitation of those methods,
- The acceptance criteria, including the rationale for setting the specific limits,
- Other products, processes, and equipment for which the planned validation is valid according to a “bracketing” concept,
- When Re-validation will be required.

4.2 The Cleaning Validation Protocol should be formally approved by the Plant Management, to ensure that aspects relating to the work defined in the protocol, for example personnel resources, are known and accepted by the management. Quality Assurance should be involved in the approval of protocols and reports.

4.3 A Final Validation Report should be prepared. The conclusions of this report should state if the cleaning process has been validated successfully. Limitations that apply to the use of the validated method should be defined (for example, the analytical limit at which cleanliness can be determined). The report should be approved by the Plant Management.

4.4 The cleaning process should be documented in an SOP.

4.5 Records should be kept of cleaning performed in such a way that the following information is readily available:

- the area or piece of equipment cleaned,
- the person who carried out the cleaning,
- when the cleaning was carried out,
- the SOP defining the cleaning process,
- the product which was previously processed on the equipment being cleaned.

4.6 The cleaning record should be signed by the operator who performed the cleaning and by the person responsible for Production and should be reviewed by Quality Assurance.

5.0 Personnel

5.1 Operators who perform cleaning routinely should be trained in the application of validated cleaning procedures. Training records should be available for all training carried out.

5.2 It is difficult to validate a manual, i.e. an inherently variable/cleaning procedure. Therefore, operators carrying out manual cleaning procedures should be supervised at regular intervals.

6.0 Equipment

6.1 The design of the equipment should be carefully examined. Critical areas (those hardest to clean) should be identified, particularly in large systems that employ semi-automatic or fully automatic clean-in-place (CIP) systems.

6.2 Dedicated equipment should be used for products which are difficult to remove (e.g. tarry or gummy residues in the bulk manufacturing), for equipment which is difficult to clean (e.g. bags for fluid bed dryers), or for products with a high safety risk (e.g. biologicals or products of high potency which may be difficult to detect below an acceptable limit).

7.0 Microbiological Aspects

7.1 The existence of conditions favourable to reproduction of micro organisms (e.g. moisture, temperature, crevices and rough surfaces) and the time of storage should be considered. The aim should be to prevent excessive microbial contamination.

7.2 The period and when appropriate, conditions of storage of equipment before cleaning and the time between cleaning and equipment reuse, should form part of the validation of cleaning procedures. This is to provide confidence that routine cleaning and storage of equipment does not allow microbial proliferation.

7.3 In general, equipment should be stored dry, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations.

8.0 Sampling

8.1 Samples should be drawn according to the Cleaning Validation Protocol.

8.2 There are two methods of sampling that are considered to be acceptable, direct surface sampling (swab method) and indirect sampling (use of rinse solutions). A combination of the two methods is generally the most desirable, particularly in circumstances where accessibility of equipment parts can mitigate against direct surface sampling.

A. Direct Surface Sampling

(i) The suitability of the material to be used for sampling and of the sampling medium should be determined. The ability to recover samples accurately may be affected by the choice of sampling material. It is important to ensure that the sampling medium and solvent are satisfactory and can be readily used.

B. Rinse Samples

(i) Rinse samples allow sampling of a large surface area. In addition, inaccessible areas of equipment that cannot be routinely disassembled can be evaluated. However, consideration should be given to the solubility of the contaminant.

(ii) A direct measurement of the product residue or contaminant in the relevant solvent should be made when rinse samples are used to validate the cleaning process.

9.0 Detergents

9.1 The efficiency of cleaning procedures for the removal of detergent residues should be evaluated. Acceptable limits should be defined for levels of detergent after cleaning. Ideally, there should be no residues detected. The possibility of detergent breakdown should be considered when validating cleaning procedures.

9.2 The composition of detergents should be known to the manufacturer. If such information is not available, alternative detergents should be selected whose composition can be defined. As a guide, food regulations may be consulted. The manufacturer should ensure that he is notified by the detergent supplier of any critical changes in the formulation of the detergent.

10.0 Analytical Methods

10.1 The analytical methods should be validated before the Cleaning Validation Study is carried out.

10.2 The analytical methods used to detect residuals or contaminants should be specific for the substance to be assayed and provide a sensitivity that reflects the level of cleanliness determined to be acceptable by the company.

10.3 The analytical methods should be challenged in combination with the sampling methods used, to show that the contaminants can be recovered from the equipment surface and to show the level of recovery as well as the consistency of recovery. This is necessary before any conclusions can be made based on the sample results. A negative result may also be the result of poor sampling techniques.

11.0 Establishment of Limits

11.1 The pharmaceutical company's rationale for selecting limits for product residues should be logically based on a consideration of the materials involved and their therapeutic dose. The limits should be practical, achievable and verifiable.

11.2 The approach for setting limits can be:

- product specific Cleaning Validation for all products;
- grouping into product families and choosing a "worst case" product;
- grouping into groups of risk (e.g. very soluble products, similar potency, highly toxic products, difficult to detect).

11.3 Carry-over of product residues should meet defined criteria, for example the most stringent of the following three criteria:

11.3.1 No more than 0.1% of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product;

11.3.2 No more than 10 ppm of any product will appear in another product;

11.3.3 No quantity of residue should be visible on the equipment after cleaning procedures are performed. Spiking studies should determine the concentration at which most active ingredients are visible;

11.3.4 For certain allergenic ingredients, penicillins, cephalosporins or potent steroids and cytotoxics, the limit should be below the limit of detection by best available analytical methods. In practice this may mean that dedicated plants are used for these products.

11.4 One cannot ensure that the contaminate will be uniformly distributed throughout the system. It is also an invalid conclusion to make the assumption that a residual contaminant would be worn off the equipment surface uniformly or that the contamination might only occur at the beginning of the batch.

11.5 In establishing residual limits, it may not be adequate to focus only on the principal reactant since chemical variations (active decomposition materials) may be more difficult to remove.

12.0 References

PIC/S document PI006-1: Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation.

End of Document

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REVISION HISTORY

Rev No.	DCC Ref No.	Author	Date of Revision	Remarks of Revision
001	-	-	01 Jan 2000	New.
002	-	-	03 Aug 2001	Change of organisation name
003	-	Terrance Ong	09 Dec 2002	Update document format.
004	212	Terrance Ong	01 Mar 2004	1) Change 3D HSA logo to 2D HSA logo. 2) Change Centre name to Centre for Drug Administration 3) Detached Revision History from Guidance Notes.
005	260	Terrance Ong	06 Sep 2004	1) Re-located Revision History to the main document.