Cleaning Validation
in
Active pharmaceutical
Ingredient manufacturing plants

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APIC Active Pharmaceutical Ingredients Committee

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1. Foreword

This Guideline has been produced by the Active Pharmaceutical Ingredients Committee (APIC) Working group.

Different organizations will be influenced by their companies and the markets that they serve in the approaches that they take and the policies that they have with respect to the subject.

It is also valuable to bear in mind that this is an area that is changing rapidly and what was considered as being acceptable 2-5 years ago is now not adequate. Therefore, companies should be aware of the need to continuously update themselves on current regulatory requirements.

2. Objective

The intention of this document has been to define a comprehensive approach to the Validation of Cleaning procedures in Active Pharmaceutical Ingredient manufacturing facilities.

Cleaning Validation in the context of Active Pharmaceutical Ingredient manufacture may be defined as:

> *The process of providing documented evidence that the cleaning methods employed within a facility consistently controls potential carryover of product (including intermediates and impurities), cleaning agents and extraneous material into subsequent product to a level which is below predetermined levels.*

It is necessary to Validate Cleaning procedures for the following reasons:

a. It is a customer requirement - it ensures the safety and purity of the product.

b. It is a regulatory requirement in Active Pharmaceutical Ingredient product manufacture.

c. It also assures from an internal control and compliance point of view the quality of the process.

3. Scope

This Document will serve to:

1. Define the basic concepts and terms associated with Cleaning Validation in the Active Pharmaceutical Ingredient industry.
2. Serve as a guide from which Masterplans, Protocols and Reports may be compiled.

Note: General validation principles and a glossary of terms also relevant to cleaning validation are detailed in the CEFIC / EFPIA Guide entitled 'Good Manufacturing Practices for Active Pharmaceutical Ingredient Manufacturers'.

It applies to sterile API's only up to the point where the API is rendered sterile.

4. Potential residues

The Active Pharmaceutical Ingredient Industry involves (in general) the manufacture of Active Pharmaceutical Ingredients by both chemical and physical means through a series of multiple step processes. Plants or individual pieces of equipment, including ancillary equipment, may be used in multi-product manufacture or dedicated to individual products.

The result of inadequate cleaning procedures is that any of a number of contaminants may be present in the next batch manufactured on the equipment such as:

1. Precursors to the Active Pharmaceutical Ingredient
2. By-products and/or degradation products of the Active Pharmaceutical Ingredient
3. The previous product
4. Solvents and other materials employed during the manufacturing process.
5. Micro-organisms

   This is particularly the case where microbial growth may be sustained by the product.
6. Cleaning agents themselves and lubricants

5. Current regulatory guidance

Refer to the reference section of this document for details of current Regulatory Guidance.

6. Cleaning validation policy

The main focus of this document will be to describe equipment and ancillary equipment / process Cleaning Validation in an Active Pharmaceutical Ingredient manufacturing plant. However, it is appropriate to start by giving a brief introduction as to how the concept of Cleaning Validation should be approached in a facility.

It is advisable for Active Pharmaceutical Ingredient manufacturing facilities to hold an official Cleaning Validation Policy. Specific department responsibilities should be outlined in this and it should be approved by senior management. This policy should serve to provide a general guideline and direction for company personnel, regulatory authorities and customers as to how the company deals with areas associated with Cleaning Validation.

The policy should incorporate the following types of statements:

- Definition of terms employed during validation i.e. rinse vs. flush vs. wash etc.
- A statement specifying what company policy is on validation of cleaning procedures related to equipment (including ancillary) and processes.
- Company policy re dedication of equipment in certain cases (if products are deemed too dangerous and / or highly active to manufacture on multi-product equipment).
- Analytical validation policy.
- The policy should also state the rational for the methods by which acceptance criteria is determined.
- Revalidation policy.

7. Levels of cleaning

The degree or level of cleaning and validation required for processes in Active Pharmaceutical Ingredient manufacturing depends largely on:

- The equipment usage (i.e. dedicated equipment or not)
- The stage of manufacture (early, intermediate or final step)
- The nature of the potential contaminants (toxicity, solubility etc.)

Each of the above three bullets must be evaluated based on the next product, not only toxicology etc. The rational for this statement is given below:

In general, the higher the potential for finished Active Pharmaceutical Ingredient contamination the greater the requirement to validate cleaning methods to ensure product safety.

Active Pharmaceutical Ingredient manufacturers may have different levels of cleaning requirements in facilities based on the stage of the process being cleaned and the subsequent product to be manufactured.

Table 1 on page 7 illustrates an example of how a company may decide on the level of cleaning between lots.

It is the responsibility of the manufacturer to demonstrate that the level of cleaning and validation performed is adequate based on each individual situation and on a justifiable scientific rational.

Cleaning should be carried out as soon as practical after the end of processing and should leave the plant in a suitable condition for next use.

Table 1: levels of cleaning

		VALIDATION REQUIRED
LEVEL 2	i.e. • Product changeover of equipment used in final step • Intermediates of one batch to final step of another	yes – essential
LEVEL 1	i.e. • Intermediates or final Step of one product to intermediate of another • Early Step to intermediates in a product sequence	progression between level 0 and 2 depending on process and nature of contaminant based on scientific rational
LEVEL 0	i.e. in-campaign, batch to batch changeover	no validation required

NB: ALL PROCESSES MUST BE EVALUATED INDIVIDUALLY

8. Elements of cleaning validation

A brief outline of the various elements of a basic cleaning validation study is given below (see also Figure 1 on page 11).

This is followed by a more detailed view of the individual elements in this section.

I. Establishment of acceptance criteria

II. Cleaning procedure

- Identification of the equipment
- characterization of the products (Previous: activity/toxicity, solubility, subsequent: dosage, lot size)
- determination and characterization of the cleaning agents

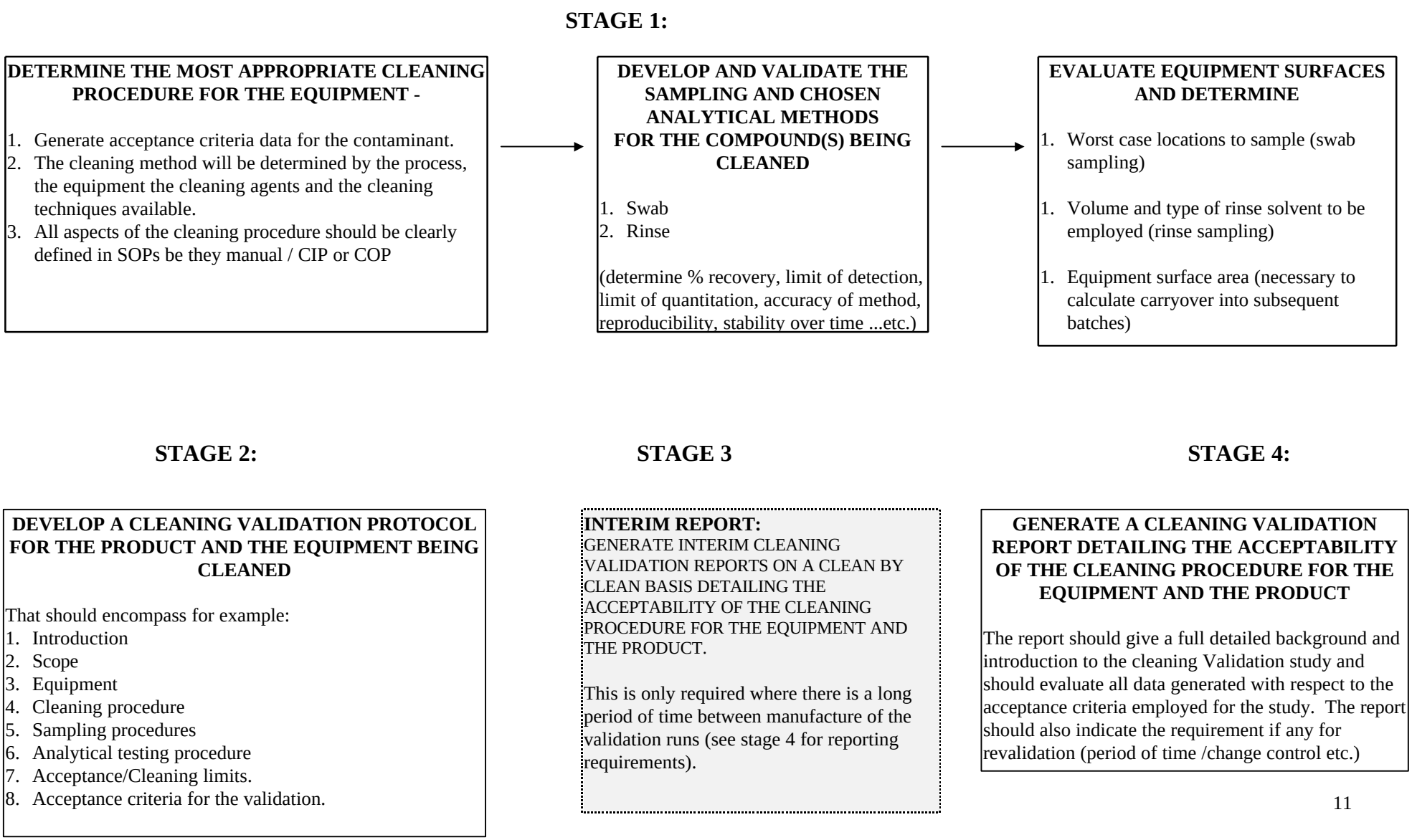
III. Analytical method and its validation

IV. Sampling Procedure and necessary validation of same

V. Validation protocol

VI. Validation report

Figure 1: Cleaning Validation Process



8.1 Establishment of acceptance criteria

The Cleaning Validation should demonstrate that the procedure consistently removes residues of the substance previously manufactured down to levels that are acceptable and that the cleaning procedure itself does not contribute unacceptable levels of residual materials to the equipment. The limits set should be practical, achievable and justifiable.

In Active Pharmaceutical Ingredient manufacture there may be partial reactants and unwanted by-products which may not have been chemically identified. Therefore, it may be necessary to focus on by-products as well as the principle reactant. Companies should decide on which residue(s) to quantify based on sound scientific rational.

8.1.1 Chemical determination

It is generally the residual Active Pharmaceutical Ingredient or intermediate, which is of greatest concern rather than reaction side products or residual impurities.

There are a number of options available when determining acceptance criteria. Where either toxicological or therapeutic data if available then calculation A or B is preferable. If data is not available for either of these calculations or if the result is more stringent calculation C should be used.

A. Limiting the level based on toxicity data.

An Acceptable Daily Intake (ADI) is calculated with suitable safety factors applied and this is converted to the maximum allowable carryover to the API.

B. Pharmacological Dose Method:

The philosophy is to reduce the levels of residual product in each piece of equipment, such that no greater than 1/1000 of the normal therapeutic dose will be present per typical dose of the next product to be run in the equipment. The validation protocol should include a calculation, which ties this philosophy to the acceptance criteria for the samples to be tested.

C. Limiting the level of product which could appear in the following products.

Limits from 10ppm up to 0.1% (based on the ICH impurity document which indicates that up to 0.1% of an individual unknown or 0.5% total unknowns material may be present in the product being tested)

Note FDA Statement on 0.1% impurities

FDA statement: P. Alcock, in Human Drug cGMP Notes, P. Motise, June 98: „...we have found that some firms have incorrectly applied as their acceptance limit the 0.1% impurity identification threshold as discussed in both the ICH impurity guideline and the U.S.P. General Notices. This application of the 0.1% impurity threshold is inappropriate because the limit is intended for qualifying impurities that are associated with the manufacturing process of related compound and not extraneous impurities caused by cross contamination. ...“) may be used depending on the stage of the process.

It is also necessary to evaluate the ability of the cleaning procedure to remove any cleaning agents introduced. The acceptance criteria for the residual-cleaning agents should reflect the absence of these materials, within the range of the capabilities of the assay and sampling methods.

The individual company must decide on the Acceptance Criteria which are justifiable for their particular situation.

8.1.2 Physical determination

There should be provision during routine cleaning for a visual examination of the equipment, verifying that it is free of visible residues. The validation protocol should include this requirement as an acceptance criteria. During validation, special attention should be given to areas that are ‘hard to clean’ (e.g. agitator shafts, thermowells, discharge valves etc.) and areas that would be difficult to verify on a routine basis.

8.1.3 Microbiological determination

Appropriate studies should be performed (e.g. swabs and/or rinse sampling) where the possibility of microbial contamination of subsequent product is deemed possible and presents a product quality risk.

8.2 Cleaning procedures

Written cleaning procedures for each piece of equipment and process[1] must be prepared. It is vital that the equipment design is evaluated in detail in conjunction with the product residues to be removed, the available cleaning agents and cleaning techniques when determining the optimum cleaning procedure for the equipment.

[1] If one cleaning procedure has been shown to be adequate for a number of products, then it is only necessary to have one cleaning SOP for those products for each piece of equipment.

Cleaning procedures should be sufficiently detailed to remove the possibility of any inconsistencies during the cleaning process.

A. Equipment parameters to be evaluated

- Identification of the equipment to be cleaned
- Difficult to clean areas
- Property of materials
- Ease of disassembly
- Fixed or not
- Etc.

B. Residues to be cleaned

- Cleaning limits
- Solubility's of the residues
- Length of campaigns
- Etc.

C. Cleaning agent parameters to be evaluated

- Preferably materials that are normally used in the process
- Detergents available (as a general guide, minimize use of detergents unless absolutely required)
- Solubility properties
- Environmental considerations.
- Health and safety considerations
- Etc.

D. Cleaning techniques to be evaluated

- Manual cleaning
- CIP (Clean-in place)
- COP (clean-out-of-place)
- Semi automatic
- Automatic
- Time considerations
- Number of cleaning cycles
- Etc.

E. Other requirements

Procedures must be determined to be operator independent i.e. rugged and reproducible, during the validation studies.

The Cleaning documentation should include the following items in order to ensure that it can be followed reproducibly and maintained subsequent to Validation.

- Detailed definition of levels of cleaning to be performed.
- Detailed description of cleaning methods.
- The necessity to inspect and verify equipment cleanliness prior to manufacture of next batch should be stated in the SOP and recorded on the batch record.
- The SOP should detail where verification of cycle parameters (if automated) and checklists (for complex manual procedures) is necessary.
- Where microbial contamination may be an issue, consideration should be given to the integrity of the vessel prior to manufacture.

Written cleaning procedures may also include additional items not specified above, these would include, as an example, the steps needed to protect the equipment from contamination after cleaning.

8.3 Sampling

In developing the sampling plan for a validation study, it makes scientific sense to
incorporate an understanding of the acceptance criteria and the limitations of the sampling method relative to the surface to be sampled.

The two methods of sampling generally employed are swab and / or rinse sampling. (If neither or these methods is shown be a scientifically sound method for testing in a specific instance then an alternative is to consider testing the next product.)

The selection of either of these techniques must be consistent with sound scientific judgment and must support the objective of the study, which is to demonstrate that the amount of residual material in the equipment has been reduced to acceptable levels.

Each method is described in brief below.

1. SWAB:

- Swab sampling does not cover the entire equipment surface area therefore sites must be chosen with care. It is important that, as a minimum, the

swab sites represent worst case locations on the equipment and that the result is then extrapolated to account for the total product contact surface area. This calculation makes it possible to make a worst case determination of potential carryover into subsequent product.

- Due to the nature of this method which employs physical forces as well as chemical forces it may be necessary to perform sampling technique evaluation.
- Swabbing efficiency (% recovery) for the swabbing method must be determined.
- It is necessary to ensure that extractables of the swab do not interfere with the sampling method.
- Using this technique it is possible to sample insoluble residues due to the physical action associated it.

2. RINSE:

- The solvent rinse occurs after cleaning has been completed
- This method is not as direct as swabbing but will cover the entire surface area (and parts inaccessible to swabs)
- It is important to ensure chosen solvent has appropriate recovery for residues being quantified
- This method allows much greater ease of sampling than swabbing
- A reduced no of samples are required to generate a carryover figure.

(Other sampling methods which may be employed in addition to swab / rinse sampling during a validation may include*:* placebo sampling, testing subsequent batches for residues, use of coupons (test pieces), etc.)

8.4 Analytical methods

In order for the analytical testing of the cleaning validation samples (swabs or rinses) to yield meaningful results, the analytical methods used should be validated. This should be documented.

The basic requirements are:

- The ability to detect the target substance(s) at levels consistent with the acceptance criteria

- The ability to detect the target substance(s) in the presence of other materials that may also be present in the sample (selectivity)

  (Companies might want to consider the following:

Where more than one impurity is suspected (which is probably the normal case in API manufacturing) a method could be proposed that is not necessarily specific for each of the impurities but detects them all together. Then additionally the assumption must be made, that the worst case (e.g. most active) impurity represents the whole residue. This is secure approach for the patients and could be accepted by the authorities. It is also an practicable approach for the industry because such methods are for example dry residue determination for non volatile impurities or TOC determination for water rinses, which are very simple methods.)

- The analytical method should include a calculation to convert the amount of residue detected in the sample to 100% if the recovery data generated indicates a recovery outside of an allowed range.

- Stability of samples over time if the time interval between removal and testing of samples potentially effects sample integrity.

8.5 Validation protocols

A Validation Protocol is necessary to define the specific items and activities that will constitute a cleaning validation study. It is advisable for companies to have drawn up a Master Validation plan indicating the overall Cleaning Validation strategy for either the product range / equipment type / entire site.

The protocol must be prepared prior to the initiation of the study and must either include or reference the documentation required to provide the following information:

- **The objective of the study**:

  What cleaning process is to be validated (indicating the product to be removed and the equipment from which it is to be removed)?

  If this study is to be employed to demonstrate the acceptability of the cleaning procedure for a group of products the rational for doing so should also be detailed here.

  The cleaning procedure(s) to be validated should be identified i.e. cleaning agents, soakage times, equipment parameters, number of cleaning cycles etc.

- **Scope of the study**:

  The company must evaluate the process and determine which residues are to be tested for and which are not to be based on sound scientific rational.

  What residues (including cleaning agents) are to be tested for, why those residues (if more residues may be present than are being tested for all residues should be under control see comments at 8.4). How many times should the study be run before a report is compiled and recommendations made.

- **Listing of the process parameters to be verified**

  This is particularly necessary when automated or semi-automated cleaning techniques are to be employed.

- **Sampling and inspection procedure to be used.**

  The types of sampling methods to be used, where the samples are to be removed from and how many samples are to be taken. Any particular requirements should also be stated i.e. for sterile sampling / sampling light sensitive products.

  An equipment sampling diagram should be referenced.

- **Personnel responsibilities during the study**

- **Test methods to be used** (should be referenced): See Section 8.4.

- **Acceptance criteria**

  Physical: see section 8.1.2
  Chemical: see section 8.1.1
  (The rational for this criterion should be given along with a calculation step.)

- **Change control:** See section 10.

- **Approval of protocol before the study.**

8.6 Validation reports

A validation report is necessary to present the results and conclusions and secure approval of the study. The report should include the following:

- Summary of or reference to the procedures used to clean, sample and test
- Physical and analytical test results or references for same, as well as any pertinent observations
- Conclusions regarding the acceptability of the results, and the status of the procedure(s) being validated
- Any recommendations based on the results or relevant information obtained during the study including revalidation practices if applicable.
- Approval of conclusions
- Review any deviations for the protocol that occurred.
- In cases where it is unlikely that further batches of the product will be manufactured for a period of time it is advisable to generate interim reports on a batch by batch basis until such time as the cleaning validation study has been completed. (Typically, in Active Pharmaceutical Ingredient Pharmaceutical manufacture, verification is deemed appropriate during development of the cleaning methods. Where products are manufactured infrequently, verification may be applied over a period of time until all measuring data has been collected for the Validation Report.)
- The report should conclude an appropriate level of verification subsequent to validation.

9. Minimum requirements

If company policy is not to validate all equipment cleaning procedures for all products then as a minimum requirement the validation policy should encompass conditions which represent the most appropriate challenges (worst case) to the procedure.

These would include, as an example, such things as:

- Removal of products which contain the products with the greatest biological activity.

- Removal of products containing the products/intermediates/byproducts with the least solubility.

These represent studies that are minimally required as part of a validation, the results from which could be used to support lesser challenges to the procedure. It is often termed product grouping.

- The maximum idle time before cleaning.

A validation program generally encompasses three consecutive successful replicates to establish that the procedure is reproducibly effective although companies should evaluate each situation individually.

Where equipment of similar size, design and construction is cleaned by the same procedure, studies need not be conducted on each unit, as long as a total of three successful replicates are done on similar pieces of equipment (equipment grouping).

Concurrent Validation may be appropriate when product is manufactured infrequently.

10. Change control

Validated cleaning procedures should be included in the change control program. This will ensure that any proposed changes are evaluated fully for their impact on the validated state of the procedure. Where deemed necessary, the proposed revised procedure may need to be validated prior to routine implementation.

Cf. Change control chapter in the CEFIC / EFPIA Guide entitled 'Good Manufacturing Practices for Active Ingredient Manufacturers'

In the absence of an intentional change to a procedure, it is reasonable to assume that properly trained operators or a properly qualified automated system will be able to execute the procedure reproducibly and obtain the desired outcome - reduction of residue to acceptable levels. There may exist special circumstances that would suggest that this assumption be verified via testing. This may be addressed by periodic reviews or re-evaluations.

11. Summary

A validation policy should be written for a plant including cleaning validation.

An cleaning validation program should contain the following elements:

1. Assess equipment and products (previous, following)
2. Assess impact of this process on routine processes. If covered under bracketing then no further validation is required.
3. Determine an appropriate cleaning agent and method
4. Determine acceptance criteria for the residue(s) (including cleaning agents).
5. Determine degree of evaluation required to validate the procedure.
6. Decide what residue(s) (including cleaning agents), are to be tested for based on solubilities, toxicities etc. and document rational behind decision.
7. Develop sampling and analytical methods for recovery and detection of residues (swab/rinse, HPLC/dry residue etc.)
8. Acceptance Criteria for the Validation
9. Compile and approve Validation protocol
10. Perform Validation Studies in accordance with protocol
11. Compile and approve a Validation report documenting studies, conclusions and recommendations.
12. Revalidation policy

12. References

ICH:

- ICH Good Manufacturing Practice Guideline for Active Pharmaceutical Ingredients. (July 23 1999)

PIC :

- Principles of Qualification and Validation in Pharmaceutical Manufacture - Recommendations on Cleaning Validation. (ref. Document PR 1/ 99 March 1999)

FDA:

- Guide to inspections of validation of cleaning processes (July 1993)
- Biotechnology inspection guide (1991)
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- Manufacture, processing or holding of active pharmaceutical ingredients, draft document, FDA, March 1998.

CEFIC / EFPIA:

- Good Manufacturing Practices for Active Ingredient Manufacturers - August 1996.

PHRMA :

- Draft PhRMA BPC Cleaning Validation Guideline. (November 1996 Edition)

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