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PRACTICAL APPROACH IN CLEANING VALIDATION: A SYSTEMATIC REVIEW

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ABSTRACT

In pharmaceutical industry there are some possibilities of contamination and cross contamination because of improper cleaning of equipment, apparatus, processing area or the starting material, this can lead to severe hazards, therefore in pharmaceutical industry we can't afford any contamination as well as cross contamination. Cleaning validation is the methodology used to assure that a cleaning process removes residues of the active pharmaceutical ingredients of the product manufactured in a piece of equipment. All residues are removed to predetermined levels to ensure the quality of the next product. Today, manufactured is not compromised by waste from the previous product and the quality of future products using the equipment, to prevent cross contamination, and as a good manufacturing practices requirement. In this article cleaning validation and cleaning validation program discussed in brief.

Keywords *– Validation, Cleaning Validation, Contamination, Clean in Place.*

1. INTRODUCTION

Validation is the documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected result. Validation is the Confirmation by examination and the provision of objective evidence that the requirements for the specific intended use are fulfilled (According to ISO). Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes (According to Food and Drug Administration FDA) [1].

1.1 Types of Validation

- Analytical Method Validation
- Process Validation
- Software Validation

• Cleaning Validation

1.2 Cleaning Validation

Cleaning validation is documented evidence which provide high degree of assurance that an approved cleaning procedure will provide equipment that is suitable for processing of pharmaceutical products or API. Cleaning means to make any article, piece of equipment and area free from dirt, marks, or any unwanted matter. In pharmaceutical industry there is a great need of cleaning of equipment apparatus and processing area. The improper cleaning can lead to contamination and cross contamination.

Validations of equipment cleaning procedures are mainly used in pharmaceutical industries to prevent cross contamination and adulteration of drug products hence is critically important. The prime purpose of validating a cleaning process is to ensure compliance with federal and other standard regulations. The most important benefit of conducting such a validation work is the identification and correction of potential problems previously unsuspected, which could compromise the safety, efficacy or quality of subsequent batches of drug product produced within the equipment. The Purpose of cleaning validation is to verify the efficacy of the cleaning methods for removal of residues of previous product, preservatives, or cleaning agents and microbial contaminants. Cleaning validation fulfills the requirement of regulatory bodies and maintains product quality and safety of consumer [2].

1.3 Advantage of Cleaning Validation

• Assurance of quality & safety

• Government regulations

• Product integrity

• Microbial integrity

• Cross contamination integrity

• Batch integrity

• Equipment reuse

• Reduction of quality costs

• Making good business sense

• Less down time, fewer batch failures and may operate / clean more efficiently

1.4 Principal of Cleaning Validation

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). 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. 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).

2. OBJECTIVE OF CLEANING VALIDATION

The objectives of equipment cleaning and cleaning validation in an Active Pharmaceutical Ingredient (API) area are same as those in pharmaceutical production area. In both these areas efforts are necessary to prevent contamination of a future batch with the previous batch material. The cleaning of 'difficult to reach' surface is one of the most important considerations in equipment cleaning validation. Equipment cleaning validation in an API facility is extremely important as cross contamination in one of the pharmaceutical dosage forms, will multiply the problem. Therefore, it is important to do a step-by-step evaluation of API process to determine the most practical and efficient way to monitor the effectiveness of the cleaning process. It is necessary to validate cleaning procedures for the following reasons

a) It is a prime customer requirement since it ensures the purity and safety of the product.
b) It is a regulatory requirement in Active Pharmaceutical Ingredient product manufacture.
c) It also assures the quality of the process through an internal control and compliance.
d) It assures as an internal control and compliance in view of quality at manufacturer end.
e) To protect product integrity.
f) To reuse the equipment.
g) It will save cost due to rejection of contaminated product & regulatory non-compliance.

3. WHY CLEANING VALIDATION REQUIRED?

To verify the effectiveness of cleaning procedures and to ensure no risks are associated with cross contamination of active ingredient or cleaning aids [3].

4. WHERE CLEANING VALIDATION NEEDED?

a) Initial qualification of process/equipment.
b) Critical change in a cleaning procedure.
c) Critical change in formulation.
d) Significant change in formulation.
e) Change in a cleaning process.
f) Change in a cleaning agent/aid.
g) Modification in equipment / chain of equipment of system.

5. WHEN CLEANING VALIDATION REQUIRED TO DO?

a) Initial qualification of process/ equipment.
b) Critical change in a cleaning procedure.

c) Critical change in formulation.

d) Significant change in formulation.

e) Change in a cleaning process.

6. ESSENTIAL PROGRAMS THAT MAINTAIN THE VALIDATED STATE AND THEIR REQUIRED ELEMENTS

- In case, introduction of new parts or repaired or modification in equipment, after completion of cleaning validation; monitor and test /challenge the respective pre-validated cleaning procedure.
- Routinely Conducted compliances, initiatives on site that maintain quality and will affect the company's ability to maintain in the validated state.
- Failure Investigation
- Change control
- Preventive maintenance
- Calibration
- Revalidation
- Important SOPs Governing Cleaning and Cleaning Validation
- Development of Cleaning SOPs (especially for manual cleaning operations)
- Equipment cleaning and use logs
- Equipment sampling procedures for cleaning assessments (e.g., swab, rinse, etc.).
- Equipment quarantine and release
- Visual inspection requirements for cleaned equipment
- Equipment Storage area / environment & Storage period

7. TYPES OF CONTAMINATIONS [4]

a) Cross contamination with active ingredients

Contamination of one batch of product with significant levels of residual active ingredients from a previous batch cannot be tolerated. In addition to the obvious problems posed by subjecting consumers or patients to unintended contaminants, potential clinically significant synergistic interactions between pharmacologically active chemicals are a real concern.

b) Contamination with unintended materials or compounds

While inert ingredients used in drug products are generally recognized as safe or have been shown to be safe for human consumption, the routine use, maintenance and cleaning of equipment's provide the potential contamination with such items as equipment parts, lubricants, chemical cleaning agents and pieces of cleaning tools such as brushes and rags.

c) Microbiological contamination

Maintenance, cleaning and storage conditions may provide adventitious microorganisms with the opportunity to proliferate within the processing equipment.

d) Contamination by cleaning or sanitizing agents:

Some pharmaceutical operations may find it necessary to use fairly toxic materials for cleaning purpose for stubborn residues. This is particularly true in the manufacture of active pharmaceutical ingredients (APIs). As such, these materials represent a potential threat as contaminants. It seems obvious that effective way of dealing with this potential problem is to use cleaning agents with the lowest toxicity that will still be effective in removing the residue in the given cleaning situation. The same factors also apply to sanitizing agents used to wipe down cleaned equipment.

e) Contamination by miscellaneous other materials:

In addition to the usual expected or anticipated list of potential contamination in a pharmaceutical operation, many other less likely materials can also contaminate products. A partial list includes equipment parts such as excipients, bristles from brushes used in packaging filling equipment, paper filters, micron filters, fibers and rubber particles from gloves, cleaning aids such as brush bristles, cloth, and cotton fibers from rags and wiping materials, lubricants.

8. CLEANING VALIDATION TEAM MEMBERS AND RESPONSIBILITIES

8.1 Validation Department

A validation officer coordinates the entire validation process by scheduling meetings and discussions with the validation team, preparing the validation protocols, monitoring the validation process, compiling and analyzing validation data and test results, and preparing the final report. All documentation associated with validation should be reviewed and approved by the validation manager for completeness and compliance with CGMP requirements. The validation officer will also develop an ongoing monitoring program (wherever applicable) to demonstrate that the processes are being maintained under control, and will support/advise on the creation and updating of all relevant systems and validation SOPs.

8.2 Production

A validation team member from the Production department participates in performing the validation steps during manufacturing processes and equipment qualification. This department should prepare the necessary SOPs for the new process or equipment and assist in the collection of validation data.

8.3 Packaging

A validation team member from the Packaging department participates in performing the validation steps during the cleaning validation of packaging equipment. The Packaging department should prepare the necessary SOPs for the cleaning of new packaging equipment and assist in the collection of validation data.

8.4 Utilities/Calibration/HVAC

A validation team member from the Maintenance department participates in performing the validation; defining the necessary equipment specifications, limitations, capacity, calibration, and maintenance requirements; and providing the necessary training on the cleaning and proper operation and maintenance of the equipment. The Maintenance department is responsible for providing the necessary utilities and equipment accessories required during the validation process. The Maintenance department is also responsible for informing the relevant departments in advance of any anticipated change to the manufacturing equipment/new inclusion and for completing equipment surface area calculations with the help of relevant drawings.

8.5 Quality Control

A validation team member from the Quality Control (QC) department is responsible for providing the necessary support for the testing and reporting of test results for validation. A support group in QC should also perform microbiological testing and environmental monitoring during the validation process. The QC department provides swabs and surface recovery data for active ingredients and cleaning agents.

8.6 Quality Assurance

A validation team member from the Quality Assurance department will be responsible for reviewing and approving the validation protocol, providing necessary support, as and when required, making an assessment in case of deviations and excursions from the protocol, and reviewing and approving the final validation report.

8.7 Product Development Laboratory

A validation team member from the Product Development Laboratory is responsible for defining the process (new product or process) to be validated and for providing technical assistance to the validation team by defining specifications, limits, and manufacturing methods.

9. CLEANING METHOD DEVELOPMENT [5]

A. SELECTION OF CLEANING LEVEL (TYPE)

Level/Degree of Cleaning

The level or degree of cleaning and validation required for the manufacturing process of drug substances mainly depends on:

i. Usage of equipment (dedicated equipment or not)

ii. Manufacturing stages (early, intermediate or final step)

iii. The nature of the potential contaminants (solubility toxicity etc.)

In case of non-dedicated drug product manufacturing facility, different cleaning procedures may exist depending on the manufacturing step and nature of the next manufacturing step to be followed in the same equipment. This results in three different levels of cleaning as explained below.

Level-1 Cleaning: [Type-A/MINOR]:

This type of cleaning take place between two batches of same product or between different strengths of the same product. For minor cleaning, cleaning validation is not required, since cross contamination is not an issue.

Example – In a manufacturing Campaign for product A, there are 3 Batches to be manufactured as shown below.

Batch 1, Batch 2, Batch 3

For a given equipment &/or equipment train, if batch 1 in the campaign is to be followed by Batch 2 in the campaign, then a level 1 cleaning is required.

Level-2 Cleaning: [Type-B/MAJOR]:

This type of cleaning take place between two products.

In this case, validation of the effectiveness of the cleaning procedure in removing residues to the required level is mandatory.

This is used between manufacturing of different Batches of different Product and / or at the end of manufacturing campaign even if same product is planned for the next campaign.

The above two degree or level of cleaning differs from each other in terms of the degree of risk associated with it, acceptance limit, degree of cleaning & method of verifying the cleaning process,

Different cleaning situation may arise during the manufacturing of drug products, such as;

i. Batch to batch changeover cleaning

ii. Changeover from early steps to intermediate of same product.

iii. Changeover from intermediate of one product to intermediate of another product.

iv. Changeover from intermediate of one product to final stage of another product.

v. Changeover from one final product to another final product

In case of non-dedicated drug substance manufacturing facility, different cleaning procedures may exist

Level-3 Cleaning: [Type-C]

Cleaning procedure to be used, after validity of ' Clean-Storage-Period' of the clean equipment stored in controlled area, before usage to product-process.

The above three degree or level of cleaning differs from each other in terms of the degree of risk associated with it, acceptance limit, degree of cleaning & method of verification of the cleaning process.

Table 1: Comparison between levels

Factor	**Level - 1**	**Level - 2**	**Level - 3**
Risk	Lowest	Highest	Lowest
Acceptance Limit	Highest	Lowest	Highest
Degree of Cleaning	Less Extensive	More Extensive	Moderate
Verification of Cleaning	Visual Inspection	Analytical Testing	Visual Inspection

Cleaning Procedures:

Standard cleaning procedures for each piece of equipment and process should be prepared. It is vital that the equipment design is evaluated in detail in conjunction with the product residues which are to be removed, the available cleaning agents and cleaning techniques, when determining the optimum cleaning procedure for the equipment. Cleaning procedures should be sufficiently detailed to remove the possibility of any inconsistencies during the cleaning process. Following parameters are to be considered during cleaning procedures.

a) Equipment Parameters to be evaluated

i.Identification of the equipment to be cleaned.
ii.'Difficult to clean' areas.
iii.Property of materials.
iv.Ease of disassembly.
v.Mobility

b) Residues to be cleaned

i. Cleaning limits
ii. Solubility of the residues
iii. Length of campaigns

c) Cleaning agent parameters to be evaluated

i.Preferable materials that are normally used in the process.
ii.Detergents available (as a general guide, minimal use of detergents recommended unless absolutely required).

iii.Solubility properties.

iv. Environmental considerations.

v.Health and safety considerations

B. SELECTION OF CLEANING METHOD

- Manual cleaning
- Semi-automatic procedures
- Automatic procedures
- CIP (Clean-in-place)
- COP (Clean-out-of-place)

Manual Cleaning Method

Although manual cleaning is a normal practice in the pharmaceutical industry, yet the use of automated cleaning usually provides reproducible results. The control system has integrated with it process control and process monitoring.

- Difficult to validate
- Most extensive and elaborate cleaning procedures are required.
- A high quality and extensive training program is required.

The risk involved in manual cleaning processes is taken care of with following:

- Proper washroom design with drying, protection and storage requirement.
- Detailed cleaning SOP.
- Training / Qualification of cleaning operators.

Automated Cleaning

The automated system is validated by challenging, and it is required that the cleaning cycle is proved to be rugged and provides reproducible results under a given range of operating conditions. The controls of an automated cleaning system also become part of the cleaning validation. Sometimes the design and construction of equipment make manual cleaning a necessity. In order to maintain good control over manual cleaning, the following parameters need to be regulated as a minimum:

A. Operator's training

B. Cleaning procedures

C. Good visual examination of the equipment

D. Change control programs

Ruggedness of the method can also be given emphasis in manual cleaning; however, reproducibility depends on strict adherence to the cleaning procedures.

Clean-In-Place (CIP) Method [6]

The CIP system involves the cleaning of large pieces of equipment at its permanent location in a configuration very similar to that utilized for production. The process is quite similar to automated cleaning, where the control system also becomes part of cleaning validation. Usually, a computer validation part becomes integrated with it if CIP is based on programmable logic control (PLC).

• Cleaning of the equipment is performed in place without disassembling

• Cleaning process may be controlled manually or by an automated program.

• Very consistent and reproducible cleaning method.

• Can be validated readily.

• Being a closed system visual inspection of all components is difficult.

Clean-Out-Of-Place (COP) Method

On the other hand, smaller equipment may be transported to a designated wash area where cleaning is performed. This practice is known as clean out of place (COP). Transportation to and from the wash area, component identifi cation, potential of cross-contamination during transfer, and storage prior to use make the task of COP more challenging than CIP. However, using automated wash systems for COP reduces the differences between CIP and COP to a significant extent, mainly due to reproducibility of the results.

• Cleaning of disassembled equipment is performed in a central washing machine.

• The washing machine also requires validation such as the temperature, ultrasonic activity, cycle time, cleaning operation sequence, detergent quantity dispensed etc.

Difficulty in cleaning the equipment:

The most difficult to clean pieces of equipment require the most intensive monitoring schedule. Easier to clean pieces require a moderate monitoring schedule. Difficulty in cleaning the product and equipment It is divided into three groups based on the degree of difficulty in cleaning the product and equipment.

1. Most difficult to clean product and equipment’s requires the most intensive monitoring schedule.

2. Easier to clean product and equipment that requires a moderate monitoring schedule.

3. Easier to clean product and equipment that requires only periodic monitoring. The monitoring program provides a mechanism to verify the capability of the cleaning procedures, the efficiency of the training program and the effectiveness of the equipment maintenance program.

C. SELECTION OF SAMPLING METHOD

Generally, there are two types of sampling that are accepted. The most desirable is the direct method of sampling the surface of the equipment, another method being the use of rinse sampling.

1. Direct surface sampling

It involves the determination of the type of sampling material used and its impact on the test data to check the interference of the sampling material with the test. Therefore, early in the validation programme, it is crucial to assure the sampling medium and solvent if they are satisfactory and be readily used. Advantages of direct sampling are that, areas hardest to clean and which are reasonably accessible can be evaluated, leading to establishing a level of contamination or residue per given surface area. Additionally, residues that are "dried out" or are insoluble can be sampled by physical removal.

2. Swab sampling [7]

After cleaning the equipment, product contact surfaces could be swabbed to evaluate surface cleanliness. Swabs used should be compatible with the active ingredients and should not interfere with the assay. They should not cause any degradation of the compound. The solvent used for swabbing should provide good solubility for the compound and should not encourage degradation.

Fig. 1: Swab Sampling

Advantages of swab sampling

- It physically removes insoluble or poorly soluble substances from the equipment surfaces.
- It is direct evaluation of equipment surface contamination.
- Adaptable to wide variety of surfaces.

- Economical and widely available.

Disadvantages of swab sampling

- This technique may introduce fibers.
- It is technique dependent of sampler.
- Difficult to implement in complex and large vessels, pipes, valves etc.

3. Rinse sampling

Sampling and testing of rinse samples for residual active ingredient is a commonly adopted method to evaluate cleanliness. This is a fairly convenient method in many cases and requires control over the solvent used for rinsing, the contact time and the mixing involved. The solvent used should be selected based on the solubility of the active ingredient and should either simulate a subsequent batch of product or at least provide adequate solubility.

A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is the "dirty pot." In the evaluation of cleaning of a dirty pot, particularly with dried out residue, one does not look at the rinse water to see that it is clean; one looks at the pot.

Fig 2: Rinse Sampling

Advantages of rinse sampling

- Easy to sampling
- Allows sampling of a large surface area and porous area.

Disadvantages of rinse sampling

- Residues may not be distributed homogeneously.
- Inability to detect location of residues.

- Rinse volume is critical to ensure interpretation of results.
- Insolubility of residues and residues
- Physically occluded in the equipment

4. Coupon sampling:

It involves the use of a coupon sampling or an actually removable piece of pipe that is dipped into high purity water to extract residues for analysis.

5. Placebo Sampling

Placebo is recognized as both potential cleaning techniques and potential sampling techniques. Placebo material comprises of all typical excipients, but not the active ingredient.

And the placebo batches were passed through a same line so that it will have possibility to scrub of the clean system.

The principle involved in placebo is that it is passed through the same pathway as the product therefore; it will have the possibility to scrub off residual product along those pathways. And it usually employed for measuring system cleanliness. It majorly depends on:

1. Excipients solubility in placebo.

2. Appropriate contact time of the placebo for collecting representative sample.

3. Coverage of the placebo in-process pathways ensures removal of the placebo from all equipment location.

4. Quantity of the placebo and residue being matched should be detectable range and the distribution of residue uniformly in the placebo ensures the detection of sample at any portion of the placebo.

Advantages

- Placebo contacts the same surfaces as the product.
- Applicable for hard-to-reach surfaces.
- Requires no additional sampling steps.

Limitations

- Difficult to determine recovery (contaminants may not be evenly distributed in the placebo)
- Lowers analytical specificity and inhibits detect ability

- Takes longer and adds expense since equipment must be cleaned after the placebo run.
- Placebos must be homogenously for each potential product.
- Residues may not be homogenously distributed.
- No direct measurement of residues on product contact surfaces. The preferred sampling method and the one considered as the most acceptable be regulatory authorities is the swabbing method.

Table 2: Major Sampling Techniques and Their Attributes.

Attributes	Swab	Rinse	Direct Surface Analysis	Coupon	Placebo
Physical Sampling of Surface	●	○	○	●	●
Robust Technique	○	●	●	●	●
Non-invasive technique	○	●	○	●	●
Adaption to hard-to-reach areas	○	●	○	○	●
Effective on flat Surfaces	●	○	●	●	●
Effective on Complex Geometries	○	●	○	●	●
Controlled area sampling possible	●	○	●	●	○
Samples are homogenous	●	○	○	●	○
Does not require contact time with surface	●	○	●	●	○
Adaptable to different solvents/materials for sample removal	●	●	N/A	●	●
Appropriate for online adaption	○	●	●	○	●
No recovery study required	○	○	○	○	○
Frequency of use	High	High	Moderate	Low	Low

D. SELECTION OF SCIENTIFIC BASIS FOR THE CONTAMINATION LIMIT (ACCEPTANCE CRITERIA) [8]

1. Acceptance criteria using health-based data

The Maximum Allowable Carryover (MACO) should be based upon the Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE) when this data is available. The principle of MACO calculation is that you calculate your acceptable carry-over of your previous product, based upon the ADE / PDE, into your next product.

Procedure

Calculate the ADE (Acceptable Daily Exposure) or PDE (Permitted Daily Exposure) according to the following equations and use either result for the calculation of the MACO.

$$\textbf{ADE} = \frac{\textbf{NOAEL} \times \textbf{BW}}{\textbf{UFc x MF x PK}}$$

$$\textbf{PDE} = \frac{\textbf{NOAEL} \times \textbf{BW}}{\textbf{F1 x F2 x F3 x F4 x F5}}$$

From the ADE / PDE number, a MACO can be calculated according to:

$$\textbf{MACO} = \frac{\textbf{ADE / PDE previous} \times \textbf{MBSnext}}{\textbf{TDDnext}}$$

MACO Maximum Allowable Carryover: acceptable transferred amount from the previous product into your next product (mg)

ADE Acceptable Daily Exposure (mg/day)

PDE Permitted Daily Exposure (mg/day)

NOAEL No Observed Adverse Effect Level (mg/kg/day)

BW Is the weight of an average adult (e.g., 70 kg)

UFc Composite Uncertainty Factor: combination of factors which reflects the inter- individual variability, interspecies differences, sub-chronic-to-chronic extrapolation, LOEL-to-NOEL extrapolation, database completeness.

MF Modifying Factor: a factor to address uncertainties not covered by the other factors

PK Pharmacokinetic Adjustments

F1-F5 Adjustment factors to account for uncertainties. Refer to EMA Guidance 2 for further explanation.

TDDnext Standard Therapeutic Daily Dose for the next product (mg/day)

MBSnext Minimum batch size for the next product(s) (where MACO can end up) (mg)

Instead of calculating each potential product change situation, the worst-case scenario can be chosen. Then a case with most active API (lowest ADE or PDE) is chosen to end up in the following API with the smallest ratio of batch size divided with TDD (MBS/TDD ratio).

If OEL data is available, the ADE or PDE can be derived from the OEL.

2. Acceptance criteria based on Therapeutic Daily Dose

When limited toxicity data is available and the Therapeutic Daily Dose (TDD) is known, this calculation may be used. It is used for final product changeover API Process —A to API Process —B.

Procedure

Establish the limit for Maximum Allowable Carryover (MACO) according to the following equation.

$$\mathbf{MACO} = \frac{\mathbf{TDDprevious} \times \mathbf{MBSnext}}{\mathbf{SF} \times \mathbf{TDDnext}}$$

MACO Maximum Allowance Carryover: acceptable transferred amount from the previous product into your next product (mg)

TDDprevious Standard Therapeutic Daily Dose of the investigated product (in the same dosage from as TDDnext) (mg/day)

TDDnext Standard Therapeutic Daily Dose for the next product (mg/day)

MBSnext Minimum batch size for the next product(s) (where MACO can end up (mg)

SF Safety factor (normally 1000 is used in calculations based on TDD).

3. Acceptance criteria based on LD50

In cases where no other data is available (e.g. ADE, OEL, TDD,…) and only LD50 data is available (e.g. chemicals, intermediates, detergents, …), the MACO can be based upon LD50 data.

Procedure

Calculate the so-called NOEL number (No Observable Effect Level) according to the following equation and use the result for the establishment of MACO (See [3] on page 53 - for reference).

$$\mathbf{NOEL} = \frac{\mathbf{LD50} \times \mathbf{BW}}{\mathbf{2000}}$$

From the NOEL number a MACO can be calculated according to:

$$\mathbf{MACO} = \frac{\mathbf{NOELprevious} \times \mathbf{MBSnext}}{\mathbf{SFnext} \times \mathbf{TDDnext}}$$

MACO Maximum Allowance Carryover: acceptable transferred amount from the previous product into your next product (mg)

NOELprevious No Observed Effect Level (mg/day)

LD50 Lethal Dose 50 in mg/kg animal. The identification of the animal (mouse, rat etc.) and the way of entry (IV, oral etc.) is important (mg/kg)

BW Is the weight of an average adult (e.g., 70 kg) (kg)

2000 2000 is an empirical constant

TDDnext Standard Therapeutic Daily Dose for the next product (mg/day)

MBSnext Minimum batch size for the next product (s) (where MACO can end up)

SFnext Safety factor

The safety factor (SF) varies depending on the route of administration (see below). Generally, a factor of 200 is employed when manufacturing APIs to be administered in oral dosage forms.

Safety factors:

Topicals: 10 – 100

Oral products: 100 – 1000

Parenteral: 1000 – 10 000

4. General Limit as acceptance criteria

If MACO calculations result in unacceptably high or irrelevant carryover figures, or toxicological data for intermediates are not known, the approach of a general limit may be suitable. Companies may choose to have such an upper limit as a policy. The general limit is often set as an upper limit for the maximum concentration (MAXCONC) of a contaminating substance in a subsequent batch.

Procedure

Establish MACOppm, based on a general limit, using the following equations.

MACOppm = **MAXCONC** x **MBS**

MACOppm Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). Calculated from general ppm limit.

MAXCONC General limit for maximum allowed concentration (kg/kg or ppm) of "previous" substance in the next batch.

MBS Minimum batch size for the next product(s) (where MACO can end up)

E.g., for a general limit of 100 ppm: MACO = 0.01% of the minimum batch size (MBS), and for a general limit of 10 ppm: MACO = 0.001% of the minimum batch size (MBS).

A general upper limit for the maximum concentration of a contaminating substance in a subsequent batch (MAXCONC) is often set to 5-500 ppm (100 ppm in APIs is very frequent) of the previous product into the next product depending on the nature of products produced from the individual company (e.g. toxicity, pharmacological activity,…).

The Threshold of Toxicological Concern (TTC) concept could be applied to intermediates or API's with no clinical (e.g. early development) or toxicological data. This concept includes three categories of products with limited or no data:

- Products that are likely to be carcinogenic;
- Products that are likely to be potent or highly toxic;
- Products that are not likely to be carcinogenic, potent or highly toxic.

The corresponding ADE's recommended for these three categories are 1, 10, 100 µg/day, respectively.

E. SELECTION OF WORST CASE

A worst-case rating study, will priorities existing drug substances, in a cleaning validation program, based on information on applicable criteria chosen by the company.

a) Hardest to clean: experience from production

b) Solubility in used solvent

c) Highest toxicity

d) Lowest therapeutic dose

e) Lowest limit (based on therapeutic doses / tox. data, batch sizes, surface areas etc.)

f) Other scientific rationales

Related to the Equipment:

For the product-specific approach, a validation protocol is compiled for every critical product that includes all types of equipment necessary for the production process. Bracketing by equipment should be done only when it is similar equipment, or the same equipment in different sizes (e.g., 300-L, 500-L and 1000-L tanks). An alternative approach may be to validate the smallest and the largest sizes separately. The worst case for a group of equipment is represented by the equipment with the larger product contact surface and the hardest-to-clean locations.

Related to the Product:

For the equipment-specific approach, a validation protocol is compiled that includes all critical products manufactured on this equipment. Only one product out of a group of products processed in a piece of equipment is selected for the cleaning validation study, based on the lowest solubility of the active ingredient and its therapeutic dose.

F. ESTABLISHING THE STORAGE PERIOD AFTER CLEANING (HOLD TIME STUDY)

The objective for establishing time limit between equipment cleaning and reuse is to ensure that the equipment remains clean till the next use. This needs demonstration that there is no microbial proliferation in cleaned equipment's during storage.

For establishing the time limit, the equipment should be dried. Initial swab samples for surface should be taken. Thereafter, the equipment should be protected as prescribed in the SOP and stored in its designated area. Periodic samples of product contact surface for microbiological contamination should be taken. (1st day, 2nd day, 3rd day etc.)

Based on the data generated establish the acceptable time limit.

G. SELECTION OF ANALYTICAL METHOD [9]

The basic requirements of the analytical methods should have the following criteria.

- The sensitivity of the method shall be appropriate to the calculated contamination limit.
- The method shall be practical and rapid, and, as much as possible use instrumentation existing in the company.
- The method shall be validated in accordance with ICH, USP and EP requirements.
- Testing method should have the ability to detect target substances at levels consistent with the acceptance criteria.
- Testing method should have the ability to detect target substances in the presence of other materials that may also be present in the sample.
- The testing 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 the allowed range.

1. SPECIFIC METHODS

- Chromatographic methods such as GC, HPLC etc.
- Thin layer chromatography
- Specific ion meter

Of the above methods, chromatography methods are the methods of choice, as they separate analytes, are highly specific, highly sensitive, and quantitative. But the methods are costly and time consuming.

High Performance Liquid Chromatography:

Almost every pharmaceutical company has an HPLC instrument, utilizing a variety of detector. These include UV, Fluorescence, Electrochemical, Refractive Index, Conductivity, Evaporate Light Scattering Detector and many others.

3. NON-SPECIFIC METHODS

Table 3: Comparison of Features of Typical Cleaning Validation Assay Methods.

Attribute	pH	Conductivity	Total Organic Carbon	HPLC	Ion mobility spectrometry	Direct surface FTIFF
Nonspecific	○	○	○	●	●	●
Does NOT detected in the presence of solvents	●	●	○	●	●	●
Require a soluble/semi-soluble residue	○	○	○	●	●	●
Requires an ionizable residue	●	○	●	●	○	●
Is not typically have any rapid/real time	●	●	●	○	●	●
Does NOT typically have any on/at-line capability	●	●	●	○	●	●
Uses reagent/mobile phase specialty gas	●	●	○	○	●	●
Required special sample preparation	●	●	●	○	●	●

For monitoring cleaning procedure generally TOC method is used. It offers at a moderate cost and in addition to its rapidity, a detection capability down to the ppb range.

Total Organic Carbon (TOC):

It is used widely in the pharmaceutical industries for various purposes. TOC is determined by the oxidation of an organic compound into carbon dioxide. The oxidation can occur through a number of mechanisms depending on the instrument being used. TOC is used for the analysis of detergents, endotoxins, biological media and poly ethylene glycol.

H. DOCUMENTATION

1. Detailed cleaning procedure(s) are to be documented in SOPs.

2. A Cleaning Validation Protocol is required to define 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 procedure.
- The number of lots of the same product, which could be manufactured during a campaign before a full cleaning is done.
- Detailed 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. 18
- Clearly defined sampling locations.
- Data on recovery studies where appropriate.
- Validated 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.
- Change Control/ Re-validation.

I. VALIDATION PROTOCOLS AND VALIDATION REPORT

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 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.

- Background
- Purpose of the validation study.
- Scope of the Validation study.
- Responsibilities for performing the validation study.
- Sampling procedure to be used.
- Testing method to be used.
- Acceptance criteria.
- Change Control.
- Approval of protocol before the study.
- Deviations

Validation Report

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

1. References to all the procedures followed to clean the samples and tests.

2. Physical and analytical test results or references for the same, as well as any pertinent observations.

3. Conclusions regarding the acceptability of the results, and the status of the procedures being validated.

4. Any recommendations based on the results or relevant information obtained during the study including revalidation practices if applicable.

5. Review of any deviations from the protocol.

6. When it is unlikely that further batches of the product will be manufactured for a period of time, it is advisable to generate reports on a batch-by-batch basis until such time.

7. The report should conclude an appropriate level of verification subsequent to validation.

An effective cleaning validation maintenance programme. When a minimum of three cleaning validation runs get completed and if the results meet the acceptance criteria, then the cleaning procedures would be demonstrated sufficiently and consistently to remove chemical and detergent residues from equipment surfaces during the study in order to meet the pre-established criteria. However, overtime and certain other factors can decrease the efficiency and consistency of the cleaning program.

They are:

1. Operator variability

2. Equipment aging and repair

3. Potential non representative results and monitoring programmes.

4. Changes to the product, equipment and process.

10. VALIDATION OF ANALYTICAL METHODS [10]

Table 4: Method validation Parameters of USP & ICH

Sr. No.	USP Parameters	ICH Parameters
1	Accuracy	Accuracy
2	Precision	Precision
3	Limit of Detection	Limit of Detection
4	Limit of Quantification	Limit of Quantification
5	Specificity	Specificity
6	Linearity & Range	Linearity & Range
7	Ruggedness	Ruggedness
8	Robustness	Robustness
9	-	System Suitability

Specificity:

Specificity is the ability to measure accurately and specifically the analyte of interest in presence of other components that may be expected to be present in the sample matrix. It is a measure of the degree of interference from other active ingredients, excipients, impurities, and degradation products.

Accuracy:

Accuracy refers to the trueness of the measurements to known values this is determined by analyzing known standards. Accuracy is a measure of exactness of an analytical method, or the closeness of agreement between the values, which is accepted either as a conventional, true value or as an accepted reference value and the value found.

Precision:

It refers to the reproducibility of the analytical method under normal operation and is normally expressed as the percent relative standard deviation for a statistically significant number of samples. According to the ICH, precision should perform at three different levels, repeatability, intermediate precision and reproducibility. Repeatability is the results of the method operating over a short time interval under the same condition (inter-assay precision). Intermediate precision is the result from with-in lab variations due to random events such as different day, analysts and equipment etc. reproducibility refers to the results of collaborative studies of the laboratories.

Limit of Detection:

The limit of detection (LOD) is defined, as the lowest concentration of an analyte in a sample that can be detected, not quantitated.

Limit of Quantitation:

The limit of Quantitation (LOQ) is defined as the lowest concentration of an analyte in a sample that can be determined with acceptable precision and accuracy under the stated operations of the method

Linearity and Range:

Linearity is the ability of the method to elicit test results that are directly proportional to analyte concentration within a given range. Linearity is generally reported as the variance of the slopes of the regression line. Range is the interval between the upper and the lower levels of analyte that have been demonstrated to be determined with precision, accuracy and linearity using the method as written.

Ruggedness:

This is a degree of reproducibility of the results obtained under a variety of conditions, expressed as percentage Relative Standard Deviation (RSD). This condition includes different laboratories, analyst, instruments, reagents, days etc.

Robustness:

It is a capacity of a method to remain unaffected by small deliberate variations in method parameters. Robustness of a method has been evaluated by varying method parameters such as pH, ionic strength, temperature, etc., and determining the effect (if any) on the results of the method. As in ICH guidelines, Robustness should be considered early in the development of a method. In addition, if the results of a method or other measurements are susceptible to variation in method parameters, these parameters should be adequately controlled and a precautionary statement included in the method documentation.

11. CLEANING OF EQUIPMENT

11.1 Dedicated and Non dedicated Equipment

In pharmaceutical industries, dedicated equipment is used for the production of only a single product. This practice markedly reduces the chances of cross-contamination. Where the same equipment is used for the production of a range of products, the prevention of cross-contamination between products becomes the main challenge in the cleaning validation effort. Dedicated equipment should be clearly identified so as to prevent potential errors during cleaning and preparation. Nevertheless, cleaning nondedicated equipment represents a clearer impediment to overcome.

The cleaning of dedicated and nondedicated equipment also gives rise to concerns. CIP systems are often used for more than one tank in a facility. Special care needs to be taken in designing CIP systems. By using appropriate valving and backflow prevention, cross contamination can be prevented. Similarly, any circulation within the CIP system should be constructed carefully and monitored closely during routine cleaning.

11.2 Minor and Major Equipment

Although there is no such terminology as minor equipment used in current good manufacturing practices (CGMPs), items such as utensils may be regarded as minor equipment.

Major equipment represents those that play a central role in production processes. Typically, the cleaning of major equipment will be the subject of specific standard operating procedures

(SOPs) and it is important to differentiate those pieces of equipment that are central to the production process from those that perform a secondary role (utensils). Material of construction should be of significant importance when establishing a cleaning validation program. CGMPs 211.65 emphasizes the material of construction as well as any substance required for operation, in which contact components, in-process materials, or drug products shall not be reactive so as to alter the safety and efficacy of the product beyond established requirements.

Equipment should not demonstrate any type of reaction with process materials, which contact them. Equipment with porous surfaces, for example, filters, filter bags, fluid bed dryer bags, membrane filters, and so on, will require thorough assessment while reviewing cleaning validation evaluations so as to ensure adequate product removal and minimize the potential for cross-contamination.

11.3 Noncritical and Critical Site of Equipment

Locations that have a tendency to endanger a single dose with a high level of contamination are called critical sites. Such locations or sites demand special cleaning emphasis. Besides ensuring that enough details are included in the cleaning procedure, the risk can be further reduced or completely eliminated by using more intensive sampling and testing plans. A more stringent acceptance criterion must also be established in this case to ensure effective cleaning validation.

11.4 Nonproduct Contact versus Product Contact Surfaces

As a matter of course, cleaning validation mainly focuses on product contact surfaces. However, in order to be more effective, programs for the elimination of cross-contamination must also address nonproduct contact surfaces. When establishing the prerequisites for nonproduct contact surfaces, the probable interactions of that area with the process must also be reviewed. This is important in order to make the cleaning program more effective.

11.5 Equipment Train: Simple and Complex

The group or collection of equipment or systems jointly functioning to carry out the production processes for a product is generally called “equipment train.” There is a direct relationship between the complexity of cleaning validation and the complexity of the equipment train. The greater the pieces of equipment in the train, or the transfers of material involved in the process, the higher the complexity of cleaning validation.

12. CLEANING OF FACILITY

1. Single-Product Facility and Multiple-Product Facility

The scenario is equivalent to that for dedicated and nondedicated equipment. Since no cross-contamination concerns exist in the case of a facility producing only a single product, the validation requirements are automatically minimized. Various challenges related to multiproduct facilities, which need to be dealt with, are elimination of cross-contamination potentials and careful monitoring of changeover of equipment from one product to another.

In addition, continuous monitoring must also be warranted to ensure that all controls and limits established are in place after accomplishment of cleaning validation.

2. Campaign Production and Batch Production

Campaign production always helps in minimizing cross-contamination issues between lots. In a multiple-products facility, campaign lots of a single product or product family are produced in the same equipment. At times, the production trot may be stopped for a part cleanup of the equipment, which is less stringent than a full cleanup. Once the campaign production is over, an intensive cleaning of the facility and equipment can be performed before starting the production of a different product [11-26].

13. CONCLUSION

The pharmaceutical industry should be free any contamination or cross contamination, it would be safe for the consumer. With the help of cleaning validation any department of pharmaceutical industry can achieve high degree of assurance regarding the cleaning, with this we can minimize any kind of contamination or cross contamination which is may be any residue of previous product, substance of machine or any microbial contamination. There is practically impossible to prove that production equipment is “clean” at the level of 100%. However, it is possible to prove that the traces of active product remaining spread through the equipment parts are within an acceptable limit and that we are capable of detecting and quantifying these trace levels. Cleaning validation provides a means of proving that the contamination levels of proving that the contamination levels have been reduced below contamination acceptable limits. Cleaning validation programme should be based on detailed cleaning procedures, a validation protocol, validated methods, a change control programme, and a validation report.

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10. DISCLOSURE OF CONFLICT OF INTEREST

The author declares no conflict of interest.

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