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LIFE CYCLE APPROACH TO CLEANING VALIDATION

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ABSTRACT: The regulatory expectations are changing day by day on the cleaning validation in Pharmaceutical industries, considering the patient safety and drug efficacy. Manufacturing of an Intermediate and Active Ingredient Pharmaceuticals involves many chemical syntheses and same equipment is being using for manufacturing of different product in multi-production facility. Equipment cleaning plays a key role in controlling the contamination, to control the potential carryover of the product, cleaning methods shall be designed effectively to reduce the previous product residue. The current good manufacturing practice regulations state that cleaning is a critical issue to ensure the product quality. Improper cleaning results the carryover of the previous product residue and leads to failure of the product, so adequate cleaning procedures should be in place to clean the equipment to provide the documented evidence. The established cleaning procedures and cleaning methods shall be validated, life cycle approach is considered for the cleaning validation process. The article discussed about the outlines of the life cycle approach for the cleaning validation.

INTRODUCTION: Equipment's which are being used or which are proposed to use for manufacturing of different pharmaceutical product shall be cleaned with appropriate cleaning procedures, the equipment's may be contaminated with previous product residue or by any other materials. The cleaning of equipment plays an important role in contamination of the subsequent product, the procedure for cleaning of equipment shall be designed to prevent the contamination of equipment, components, utensils and containers.

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The cleaning procedure shall be validated to prove that the system consistently does as expected and produces a result that consistently meets the predetermined specification. To benefit of performing the cleaning validation is to avoid the potential problems which affect the product quality of subsequent drug product produced in the same equipment/ components.

Cleaning is not a recent activity in pharmaceutical industries and it a part of Good Manufacturing Practice (GMP), FDA first discussed about the equipment cleaning in 1963 GMP regulations, part of 133.4 stated as "Equipment shall be maintained in a clean and orderly manner". In 1978 cGMP regulations, the same section was captured in the FDA 21 CFR part 211.67; the main cause is to prevent the contamination of drug product.

The guidelines on "cleaning validation in Active pharmaceutical Ingredients manufacturing plants" was released by APIC (Active Pharmaceutical Ingredient committee) in September, 1999. Later the guidance was revised in Dec-2000 by APIC (A sector group of CEFIC – The European Chemical Industry Council). The same guidance being followed by the industries while proceeding for a cleaning validation. But during all these years, the requirement of cleaning validation and understands are being increased.

Hence with the oversight, APIC has revised its guidance on cleaning validation in the year 2014. The new guideline scope has been increased to "Control of the cleaning process" along with the existing and suggests us to use ADE (Acceptable Daily Exposure) is now recommended to define the MACO (Maximum Allowable Carry Over) of APIs in multipurpose equipments.

DISCUSSION: The science based and risk based life cycle approach to the manufacturing process validation describes in USFDA "Guidance for industry – Process Validation: General principles and Practices" given a new approach with three stages process validation to validate the procedures, stage – 1: Process design, Stage – 2: Process Qualification and stage – 3: Continues process verification. This life cycle approach can also applicable to cleaning validation as the cleaning is one type of process. The major focus of process validation is quality with consistent results from batch to batch and the different process for different products, the major focus of cleaning validation is to clean the residue of previous product to below the acceptance criteria and most of the cleaning procedures are same for an equipment/ component.

Life Cycle approach to the cleaning validation: As explained in the "Guidance for industry – Process validation: General principles and industries", FDA is proposing three stage validation approach, Stage – 1: Process design, stage – 2: Process qualification and the stage – 3: Continues process verification. This approach is applicable to not only for the manufacturing process for a product but also applicable to the other processes which are following and validating. Equipment cleaning process is one of them, following to clean the equipment for good quality of product, the process which is following for cleaning of equipments were validating to provide the documented evidence and to prove that the procedures are producing consistently good results as per the set acceptance criteria. The **Fig. 1** gives a brief idea of life cycle approach,

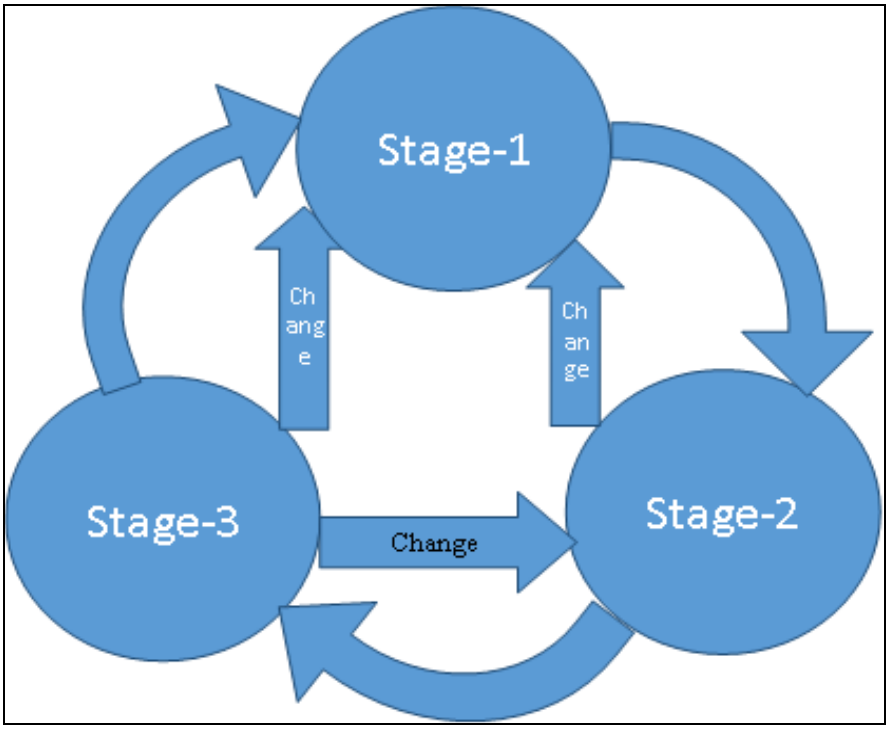
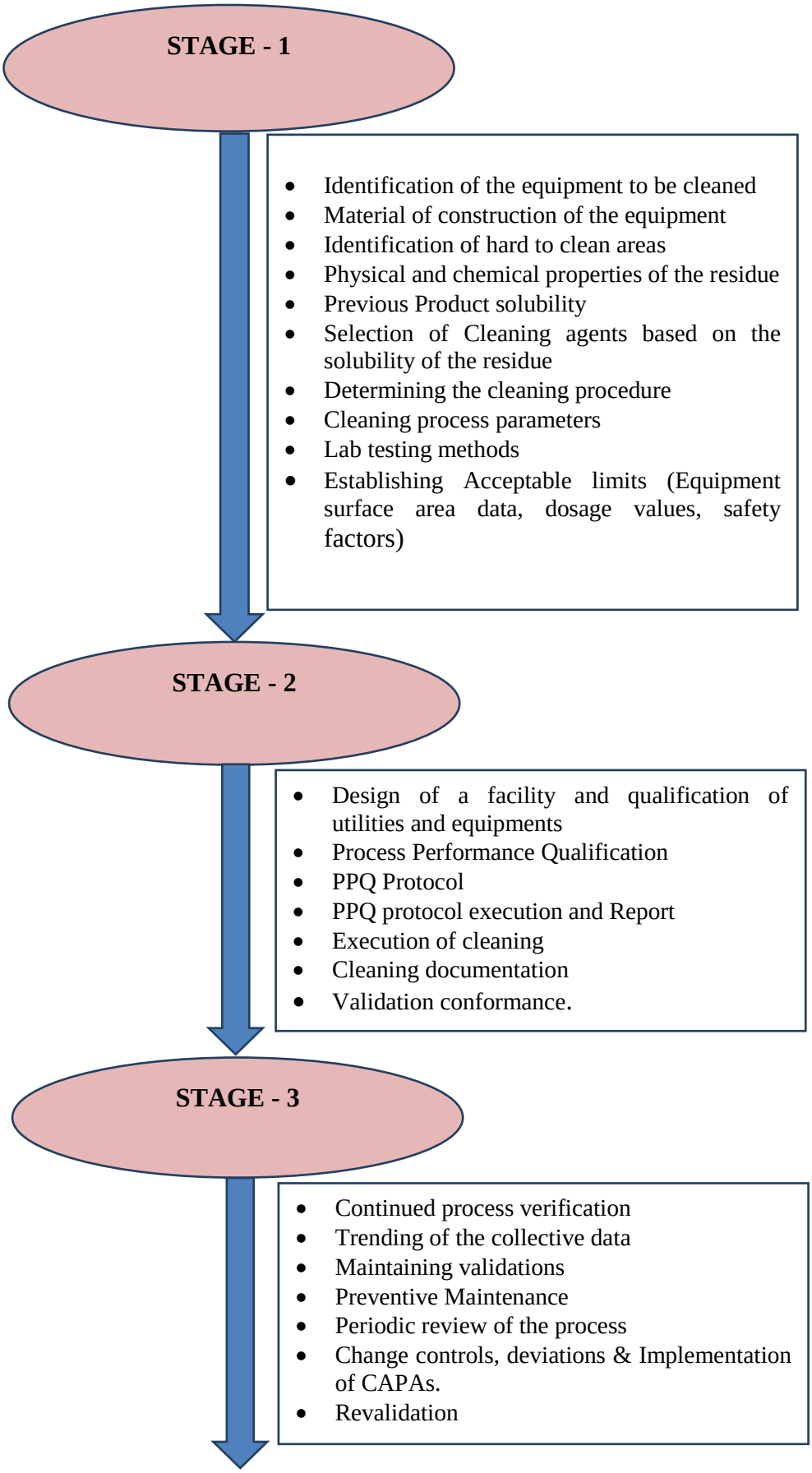


FIG. 1: LIFE CYCLE STAGES FOR CLEANING VALIDATION PROCESS

Key Elements to be considered for each stage with flow chart.



Stage - I: Process design: In this stage the main aim is to design the cleaning process for removal of previous product residue to a certain level. The main aim of this stage is to collect the information about the residue to be cleaned or the product shall be cleaned. Develop the product change over cleaning procedure for product contact parts/ equipments, how the equipment shall be cleaned, what process parameters shall be considered critical, at what level the cleaning is acceptable, what reagents. Cleaning agents are suitable/ considered what laboratory method is suitable. See below for this stage requirements

- Identification of the equipment to be cleaned
- Material of construction of the equipment
- Identification of hard to clean areas
- Physical and chemical properties of the residue
- Previous Product solubility
- Selection of Cleaning agents based on the solubility of the residue
- Determining the cleaning procedure
- Cleaning process parameters
- Lab testing methods
- Establishing Acceptable limits (Equipment surface area data, dosage values, safety factors)

The cleaning procedure shall cover all the components which are connected to the particular equipment. Example if we consider a reactor for cleaning, the procedure should include the cleaning of the connected lines, like vapour line, process lines, heat exchanges, process vessels, etc.

Table 1 gives the brief idea of the equipment with identifications and to assess the hard to clean area which helps in identifying the sampling locations and to collect the data of the particular equipment like, major components of the equipment, material of construction (MOC), surface area of the equipment (which helps in calculating the acceptance criteria)

TABLE 1: EQUIPMENT DETAILS WHICH ARE TO BE CLEANED ALONG WITH THE SURFACE AREA

S. No	Equipment Identification No	Main Parts of the equipment	Surface area
1	GL Reactor, GLRXXX MOC: Mild steel Glass Line		_____cm^2
2	SS Reactor, SSRXXX MOC: Stainless steel		_____cm^2
3	Centrifuge, SSCFXXX MOC: Stainless steel		_____cm^2
4	Tray drier, SSTDXXX MOC: Stainless steel		_____cm^2
5	Rotocone vacuum drier, GLRCVDXXX MOC: Glass lined		_____cm^2
6	Multi Miller, SSMMXXX MOC: Stainless steel		_____cm^2
7	Sifter, SSSFXXX MOC: Stainless steel		_____cm^2
8	Blender, SSBLXXX MOC: Stainless steel		_____cm^2
9	Utensils: Sampler, scoops, scrappers		---

Identification of Hard to clean area: Identification of "Hard to clean area" or critical area to clean is a one of the important task, where the cleaning activity is unable to perform and where at least the visual inspection was unable to perform can be considered as "Hard to clean area" or critical area to clean. Hard to clean areas assessment will help in designing the cleaning procedure and in selection of sampling locations. A template **Table 2** will explain how the hard to clean area can be identified which is difficult to clean in an equipment.

Selection of Solubility criteria: The **Table 3** helps to select the cleaning agent, the minimum criteria to select a cleaning agent is the product should be at least freely soluble (1 gram of material required less than 1 ml of solvent) or soluble (1 gm of material required 10 to 30 ml of solvent), freely Soluble and soluble solvent whichever is effective

and economical will be used for cleaning. The capability to clean the equipment is related to the solubility of the materials being removed in washed and stage of cleaning. Materials which are soluble freely in water can be rapidly reduced in concentration through repetitive dilution of the surface with additional washes.

The cleaning agent shall be selected based on the properties of the agent with scientific justification. Below given are some properties which shall be considered before selecting the cleaning agent.

- Non corrosive cleaning agent shall be selected; it should not be reacted with the equipment surface.
- Usage of Class-1 solvents(Benzene, Carbon tetrachloride, 1, 2 - Dichloroehtane, 1, 1-Dichloroethene & 1, 1, 1-Trichloroethane) shall be avoided (Known human carcinogens, strongly suspected human carcinogens, and environmental hazards)
- Easy to handle the cleaning agent.
- The solubility shall be checked for the particular residue in the equipment.

Proper selection of these agents and parameters could help in developing a system that is more easily validated, thus simplifying cleaning validation efforts immensely, since the cleaning agent and parameters are difficult to change once they are validated, and can have an important influence on the operating procedures and therefore on the cost of manufacture, it is important to understand and evaluate the various available options at an early stage.

TABLE 2: TEMPLATE FOR "HARD TO CLEAN AREA" ASSESSMENT, AS AN EXAMPLE REACTOR IS TAKEN FOR CLEAR EXPLANATION

Name of the Equipment	Product contact areas		Accessibility of cleaning	Accessibility of visual inspection	Category
Reactor		Top dish	It's difficult to clean	Not possible	Difficult
		Shell	Cleaning is possible as the cleaning agent is contact to this area.	Possible	Easy
		Bottom dish	Cleaning is possible as the cleaning agent is contact to this area.	Possible	Easy
	-Top dish -Shell -Bottom dish -Agitator -Baffles	Agitator	Cleaning is possible as the cleaning agent is contact to this area.	Possible, however the bottom of the agitator is not visible for cleanliness	Medium
		Baffles	Cleaning is possible as the cleaning agent is contact to this area.	Possible, however the place near the bolts and bottom part of the baffles are not visible	Medium
	-Valves -Process lines	Valves	Cleaning is possible as the cleaning agent is contact to this part and the valves can be separated from the equipment and can clean manually	Possible	Easy
		Process lines	Cleaning is possible as the lines can be separated from the equipment and can clean.	Not Possible	Medium

TABLE 3: TEMPLATE GIVES THE IDEA OF THE PRODUCT SOLUBILITY CRITERIA WHICH HELPS IN THE SELECTION OF THE CLEANING AGENT TO REMOVE THE PREVIOUS PRODUCT RESIDUE

Product	Active material to be cleaned	Very soluble (1 gm of material required Less than 1 ml of solvent)	Free soluble (1 gm of material required 1 to 10 ml of solvent)	Soluble (1 gm of material required 10 to 30 ml of solvent)	Sparingly soluble (1 gm of material required 30 to 100 ml of solvent)	Slightly soluble (1 gm of material required 100 to 1000 ml of solvent)	Very slightly soluble (1 gm of material required 1000 to 10000 ml of solvent)	Practically in soluble (1 gm of material required more than 10000 ml of solvent)
X	Initial raw material Reaction mass Active substance							

Equipment cleaning process: Now a day's pharmaceutical industries are increasing using the multipurpose equipments for manufacturing of different products, it is very important to establish evidence that the cleaning procedure is effective, the cleanliness of the equipment is to minimise the risk of cross contamination of the subsequent product using the same equipment used for previous product. To clean properly we need to understand the below

- What equipment to be cleaned,
- What cleaning agents shall be used,
- How much quantity shall be taken for cleaning,
- How to use the cleaning agent properly,
- How the cleaning shall be done,
- How to check the equipment cleaning,
- What standard operating procedures shall be considered,
- What the process parameters like temperature (heating/ cooling), pressure, time etc. shall be followed during cleaning,
- To know the previous product and subsequent product details,
- Who should clean,
- What are the acceptance criteria?

To design the cleaning procedure, above points shall be considered along with the hard clean areas, the cleaning procedure should have the explanation whether the cleaning shall be done by manually or by mechanically. The cleaning procedure is the actual performance of cleaning of the manufacturing equipment, the procedure must reliably reduce levels of all potential contaminants on product contact surfaces including the previous product residue, cleaning agent residue and the microbial contaminants to the defined acceptance criteria limits. The cleaning procedure should clearly explain what type of procedure using to clean the particular equipment, there are two types of cleaning procedures were categorized, one is COP "Clean out of place" and CIP "Clean in place".

COP "Clean out of place" means the equipment will be dismounted and disassembled and the parts will be cleaned manually and returned to its original place. CIP "Clean in place" means the equipment will be cleaned without dismounted and disassembled and the cleaning will be performed with an automatically specific system.

Lab Testing Methods: The analytical method which was selected shall be validated in combination with the sampling methods used to show the contaminants can be recovered from the equipment surface. The analytical method shall be selected to detect the residue like UV (ultra violet), HPLC (High Performance liquid Chromatogram), GC (Gas Chromatogram), TLC (Thin Layer chromatography), etc... Regulatory accepts the specific methods; nonspecific methods shall be used with proper justification.

For the swab and rinse methods, the percentage recovery and the effectiveness of the recovering residue from the equipment surface of the residue shall be determined.

Solution of the known concentration of a product shall be applied on the stainless steel and glass lined plate of 10 x 10 cm^2 or 5 x 5 cm^2 or 3 x 3 cm^2 (area of the plate which is used for recovery study, the same shall be considered for acceptance criteria calculations) and allow the plate for drying for few minutes, swab the plate with the help of swab sticks and dissolve in the diluents. The diluents shall be selected based on the solubility criteria. Allow the swab sticks to dissolve properly and analyse as per the selected method. Calculation of the recovery factor

$$\text{Percentage recovery} = \frac{100 \times \text{sample concentration}}{\text{Standard concentration}}$$

The percentage recovery will be used in the swab and rinse calculations to determine the acceptance criteria of swab and rinse. Generally the percentage of the recovery study will be 80 % to 120 %.

Acceptance Criteria: As per the APIC (Active Pharmaceutical Ingredients Committee) "Guidance on Aspects of cleaning validation in Active Pharmaceutical Ingredient Plants – May 2014", companies must demonstrate during validation during validation that the cleaning procedure routinely employed for a piece of equipment limits potential carryover to an acceptable level. The limits established must be calculated based on the sound scientific rational.

Different approached to set the cleaning validation limits, for setting the swab and rinse limits MACO shall be calculated. Calculating of MACO having different methods.

1. Using health based data, ADE (Acceptance Daily Exposure)

2. Based on the Products therapeutic daily dose

3. Based on the Lethal Dose value (LD_{50})

4. General Limit based on maximum concentration and batch size

Acceptance criteria using health based data: Acceptable Daily Exposure: In 2010, the ISPE (International Society of Pharmaceutical Engineering) published its Risk-MaPP (Risk Based Manufacture of Pharmaceutical products) Baseline - "Pharmaceutical Guide, Volume - 7, First Edition". The guide introduced the ADE as the starting point for evaluating the risk to both patients and workers in the manufacture of pharmaceutical products in shared facilities.

The Risk-MaPP guide defines the ADE as the most appropriate and accurate assessment of the potential hazard presented to both patient and the worker from the active drug being manufactured, due to the ADE is based on all the available toxicological and clinical data of the drug substance.

Later, the ICH Q3D "Elemental impurities" and in European Medicine Agency (EMA)- EMA/CHMP/ CVMP/ SWP/ 169430/ 2012-"Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" issued a guidelines to implement the PDE (Permitted Daily Exposure) for assessing the risk of cross contamination in shared facilities to set the limits. For cleaning validation, most of the companies following APIC – Cleaning validation in API issued in May-2014 are following. As defined in the APIC,

The acceptance criteria preferably should be based on ADE (Acceptable Daily Exposure) calculations where ever the data is available. The Acceptable Daily Exposure defines a limit at which a patient may be exposed every day for a lifetime with acceptable risk related to adverse health effects. To derive the MACO (Maximum allowable carryover) Acceptable Daily Exposure (ADE) values shall be known, calculation of Acceptable Daily Exposure of APIs and intermediates limits can be done by the toxicology professionals internal to a company or expert consultants to set the limits. The justification of the calculations should be documented.

TABLE 4: COMPARISON OF PDE (PERMITTED DAILY EXPOSURE) AND ADE (ACCEPTABLE DAILY EXPOSURE)

PDE (Permitted Daily Exposure)	ADE (Acceptable Daily Exposure)
Equation of PDE $\frac{\text{NOAEL x Weight adjustment}}{\text{F1 x F2 x F3 x F4 x F5}}$ F1: A factor (values between 2 and 12) to account for extrapolation between the species F2: A factor of 10 to account for variability between individuals F3: A factor 10 to account for repeat –dose toxicity studies of short duration, i.e. less than 4 weeks F4: A factor (1-10) that may be applied in cases of severe toxicity. F5: A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.	Equation of ADE $\frac{\text{NOAEL x BW}}{\text{UFc x MF x PK}}$ UFc – Composite Uncertainty factor (F1 x F2 x F3 x F4 x F5) MF – Modifying Factor (1 or 10) - A factor to address uncertainties not covered by the other factors PK - Pharmacokinetic Adjustments

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

BW - 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

So ADE = $\frac{\text{PDE}}{\text{MF x PK}}$.

Modifying Factor:

- Extrapolation to sick population is required when clinical data is available on healthy population only.
- Factor value 10 is assigned (for conversion), otherwise assign 1.
- The factor value can be assigned for product with high toxicity.

Pharmacokinetic Adjustments:

- Pharmacokinetic correction factor from route to route extrapolation.
- Applicable only when route specific bioavailability differs significantly >40 %.
- If there is no bioavailability data available for concerned route, 100 % respirable absorption shall be considered as default and following correction factor to be derived.

Uncertainty factor:

TABLE 5: F1 SPECIES EXTRAPOLATION FACTOR

Value	From (Animal)	To (Human)
5	Rat	Human
12	Mice	
2	Dogs	
2.5	Rabbits	
3	Monkeys	
10	Other animals	

If NOAEL data is present on Rat, 5 shall be place on F1 position in the equation.

F2: Individual variability factor: A factor of 10 to account for variability between individuals. 10 are used consistently, by default, 10 to be entered at the place of F2 in the equation.

F3: Repeat dose toxicity study factor:

- A factor 10 to account for repeat dose toxicity studies for short duration, i.e. less than 4 weeks.
- Lesser duration - Higher the factor value, longer duration – Lower the factor value.
- Factor value varies from 1 to 10.

F4: Severe Toxicity study factor:

- The factor that may be applied in case of severe toxicity
- Toxicities like non-genotoxic, carcinogenicity, neurotoxicity or teratogenicity come under sever toxicity.
- Factor value varies from 1 to 10 depending on the level of reproductive toxicity is associated with or without maternal toxicity.

TABLE 6: VALUES OF REPEAT DOSE TOXICITY STUDY

Value	Study duration in rodents (i.e. Rats, Mice & Mouse)	Study duration in non-rodents (i.e. Rabbits, cats, dogs, monkeys)
1	1 year (also in Rabbits)	7 years
2	6 months	3.5 years
5	3 months	2 years
10	For shorter duration i.e. less than 4 weeks	
1	Reproductive study in which whole period of organogenesis is covered	

TABLE 7: VALUES OF SEVERE TOXICITY

Value	Reproductive toxicity condition
1	Fetal toxicity associated with Maternal toxicity
5	Fetal toxicity without Maternal toxicity
5	Teratogenicity with Maternal toxicity
10	Teratogenicity without Maternal toxicity

F5: Database incompleteness factor (Availability of NOAEL or LOAEL):

- This factor may be applied in the No Observed Adverse Effect Level (NOAEL value is absent) was not established.
- When only LOEL (Lowest Observable Effect Level) is available, factor value shall be 10.
- Severity of the toxicity should be considered while assigning factor value

$$\text{MACO} = \text{Maximum Allowable carryover} = \frac{\text{ADE in mg} \times \text{MBS in mg}}{\text{TDD in mg}}$$

ADE -Acceptable Daily Exposure
MBS -Minimum batch size of the subsequent product
TDD -Maximum daily dose of the subsequent product.

MACO Based on the Products therapeutic daily dose: This is a traditionally approach generally using for product changeover from one API to another API when the limited toxicity data is available.

$$\text{MACO (Ppm)} = \frac{\text{Minimum TDD of previous product} \times \text{Minimum Batch Size of subsequent product}}{\text{Safety factor} \times \text{Maximum TDD of subsequent product}}$$

Safety factor shall vary depending dosage from
Topical – 1/10 to 1/100
Oral – 1/100 to 1/1000

Parental – 1/1000 to 1/10000
Research – 1/10000 to 1/100000

MACO Based on the Lethal Dose value (LD_{50}): This approach follows when only lethal dosage value is available, to derive the MACO value NOEL should be calculated as follows:

$$NOEL = \frac{LD_{50} \times \text{Weight of an average adult}}{2000 \text{ (Empirical constant)}}$$

$$MACO\ (ppm) = \frac{NOEL \text{ of previous product} \times \text{Minimum Batch size of subsequent product}}{\text{Safety factor} \times \text{Maximum TDD of subsequent product}}$$

MACO – General Limit based on maximum concentration and batch size:

MACO = MAXCONC x Minimum batch size of the subsequent product

Sampling Methods: Two sampling methods are generally used to assess the level of cleaning, 1) Direct sampling –Swab sampling and 2) Indirect sampling – Rinse sampling

Swab sampling method: 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 interface with the assay. They should not cause any degradation of the compound. The solvent used for swabbing should provide good solubility for the product and should not encourage the degradation. Advantages of the direct contact part sampling are that the hard to clean area and which are reasonably accessible can be evaluated. Once the equipment cleaning was completed

Swab sampling can be performed using the swab sticks (if the sampling area is accessible), if the selected sampling location is not accessible to perform with the swab sticks, the swab samplers will be helpful to perform the swab sampling. The below figure shows an image of swab sampler.

FIG. 2: SWAB SAMPLES

The stencil shall be designed as per the recovery factor, if the recovery factor was validated with 10 x 10 cm plate, the stencil also should be same to perform the swab sample. Swab sampling shall be done by using the swab sticks. The main disadvantage of this sampling method is not possible to sample some of the hard to clean areas.

Swabbing is commonly used sampling technique, to derive the swab limit, the surface area of the equipments and recovery factor values were required along with the MACO.

$$Swab\ (ppm) = \frac{MACO \times R_f \times \text{Swabbed surface area}}{\text{Total surface area} \times \text{Disorbent volume}}$$

MACO -Maximum Allowable Carry Over
R_f -Recovery factor:
Recovery factor shall be validated by spiking the analyte with known concentration to determine the recovery.

The recovery study shall be done with specified area, the same are shall be used for sampling for regular cleaning validation.

Swabbed surface area: The area which was validated with the recovery factor, the same area shall be considered for the swab sampling. Example: 10 x 10 cm is validated the recovery factor, the same area shall be taken for sampling.

Disorbent volume: The quantity of disorbent volume which was taken in recovery study, the same quantity shall be considered for swab sampling.

Rinse Limit: After the cleaning activity was completed, the rinse sampling can also be determined to calculate the residue amount in the equipment. The rinse sampling method is based on the analytical determination of a sample of the last rinsing solvent used in the cleaning procedure. The solvent used should be selected based on the solubility of the product and should either stimulate a subsequent batch of the product. The rinsing method is not a direct sampling method like swabbing but the rinsing will cover the entire surface area of the equipment. The main advantage of the rinse sampling method will cover the entire surface area of the equipment including the difficult to reach area.

$$\text{Rinse (ppm)} = \frac{\text{MACO} \times R_f}{\text{Rinsed volume}}$$

Comparison of the MACO, Swab and Rinse values for ADE (Acceptable Daily Exposure), TDD (Therapeutic daily dose), lethal dose and general limit basis with the below example.

For Example: The values of product A TDD is 250 mg NOAEL value is 430 mg/ kg/ day, Uncertainty Factor (UFc):F1 value is 5, F2 value is 10, F3 value is 1, F4 value is 5, F5 value is 1, Modifying Factor is 10, Pharmacokinetic Adjustment is 1 and the Product B TDD is 500 mg.

Recovery factor for stainless plate is 104 % and Glass line is 102 %, Swabbed surface area is 5 x 5 cm^2, Shared equipments surface area is 75000 cm^2, Rinsed volume is 10 litres, Safety factor for oral is 1/1000, Lethal dose is 2000 mg/ kg and average body weight is 70 kg and the general limit is considered as 10 ppm.

Based on ADE calculations:

$$\text{ADE (Acceptable Daily Exposure)} = \frac{430 \times 70}{(5\times10\times1\times5\times1)\times10\times1} = 12.04 \text{ mg/ day}$$

$$\text{MACO} = \frac{12.04 \times 50 \times 1000 \times 1000}{500} = 1204000 \text{ mg}$$

$$\text{Swab} = \frac{1204000 \times 102 \times (5 \times 5)}{75000 \times 10} = 4093.6 \text{ mg}$$

$$\text{Rinse} = \frac{1204000 \times 102}{10 \times 1000} = 12280.8 \text{ mg}$$

Based on therapeutic dose values:

$$\text{MACO} = \frac{250 \times 50 \times 1000 \times 1000}{1000 \times 500} = 25000 \text{ mg}$$

$$\text{Swab} = \frac{25000 \times 102 \times (5\times5)}{75000 \times 10} = 85 \text{ mg}$$

$$\text{Rinse} = \frac{25000 \times 102}{10 \times 1000} = 255 \text{ mg}$$

Based on Lethal Dose:

$$\text{NOEL (No Observed Effect Level)} = \frac{2000 \times 70}{2000} = 70 \text{ mg/ day}$$

$$\text{MACO} = \frac{70 \times 50 \times 1000 \times 1000}{1000 \times 500} = 7000 \text{ mg}$$

$$\text{Swab} = \frac{7000 \times 102 \times (5 \times 5)}{75000 \times 10} = 23.8 \text{ mg}$$

$$\text{Rinse} = \frac{7000 \times 102}{10 \times 1000} = 71.4 \text{ mg}$$

Based on General Limit (10 ppm):

10 ppm = 0.001 % = 0.00001 mg

$$\text{MACO} = 0.00001 \times 50 \times 1000 \times 1000 = 500 \text{ mg}$$

$$\text{Swab} = \frac{500 \times 102 \times (5 \times 5)}{75000 \times 10} = 1.7 \text{ mg}$$

$$\text{Rinse} = \frac{500 \times 102}{10 \times 1000} = 5.1 \text{ mg}$$

TABLE 8: COMPARISON OF VALUES (MACO/ SWAB/ RINSE) IN DIFFERENT APPROACHES

	Based on ADE	Based on therapeutic dose	Based on Lethal Dose	General Limit
ADE/ NOEL	ADE – 12.04 mg	---	NOEL – 70 mg/ day	---
MACO	1204000 mg	25000 mg	7000 mg	500 mg
Swab	4093.6 mg	85 mg	23.8 mg	1.7 mg
Rinse	12280.8 mg	255 mg	71.4 mg	5.1 mg

Based on the above table, it is proved that the ADE (Acceptable Daily Exposure) approach is very relaxed limits compared with the other approached (i.e. Therapeutic dose, lethal dose and general limits approaches).

Stage 2: Process Qualification: As per the guidelines "Guidance for industry – Process validation: General principles and practices, 2011 by FDA" Stage 2, process qualification stage has two elements.

- Design of a facility and qualification of the equipments and utilities
- Process performance qualification.

Design of a facility and qualification of the equipments and utilities: Equipments which are considered for cleaning validation and CIP systems which are using during cleaning of the equipment and the laboratory instruments shall be ensured for completion of the qualification activity (Installation Qualification, Operation Qualification & Performance Qualification). The following points shall be ensured before starting the cleaning validation activity.

- All direct impact utilities for the cleaning must be qualified, generation and distribution systems (nitrogen system, compressed air system, water system, etc.) of the utility must be approved prior to use for cleaning of equipment.
- If the final rinse is with the water, the water must be same or better quality as that used for the manufacturing process.
- Solvents used for the cleaning of equipment must be from the qualified vendor and only approved material only shall be used.
- Spray devices (if CIP system is using for cleaning) used for cleaning should be qualified for ensuring proper coverage.
- Computerized systems which are using for the operation and monitoring of the cleaning process must be qualified.
- The instruments which are using for process monitoring (like gauges, indicators, sensors, flow meters, etc…) must be calibrated.
- Analytical methods must be validated.
- Persons who are involved in the cleaning operation must be trained.

Process Performance Qualification: Process performance qualification involves developing the cleaning validation protocol including acceptance criteria for the residue limits based on the scientifically justified. The cleaning validation is performed under cGMP conditions with the purpose of demonstrating controls over the cleaning process conducted during the routine cleaning operations. Cleaning validation is performing under routing commercial manufacturing conditions by the trained operators for the commercial purpose. Before starting the cleaning activity the following shall be ensured.

- Stage 1 supporting documents.
- Analytical method readiness (Analytical instrument qualification, Analytical method validation and Recovery studies).
- Training for the persons.
- Equipment cleaning procedure.
- Process equipment (Equipment qualification).
- Utility system readiness (Water qualification, Nitrogen and compressed air qualification, instruments like gauges, sensors, etc… calibration).
- Vendor qualification (Vendor approval for the cleaning agents).
- Cleaning validation protocol should involve the following but not limited to:

  - Back ground,
  - Scope and Objective,
  - Responsibilities,
  - List of Equipments,
  - Cleaning procedure,
  - From which product to which product cleaning is planned,
  - Cleaning agent,
  - Sampling methods,
  - Sampling locations,
  - Analytical procedures,
  - Acceptance criteria,
  - Equipment and sampling location diagram,
  - Documentation,
  - Revalidation,
  - Cleaning validation report.

Completion of a validation study should have minimum three runs of one product to another change over cleaning, after completion of single run an interim report shall be approved by stating, followed cleaning procedure is as per the approved procedure, the swab and rinse results are meeting the acceptance criteria, conclusion of the single run. A complete validation report shall be prepared after completion of successful three runs and the validation report is necessary to present the results and conclusion and approval of the cleaning validation study. The report should have the following but not limited to:

- Reference protocol details,
- From which product to which product cleaning has been done,
- Sampling and analysis were done as per the protocol,
- Physical and analytical test results,
- Summary to the procedures used to clean,
- Conclusion regarding the acceptability of the results and the status of the procedures being validated,
- Any other recommendations based on the cleaning validation during the study.

Revalidation: A revalidation shall be recommended when any change that might impact the cleaning process or impacting the cleaning validation study. Significant changes should follow satisfactory review and authorization of the documented change proposal through the change management system. The review should include consideration of revalidation of the cleaning procedure.

Stage 3: Continues Process Verification: The main objective of the stage 3 is continual assurance that the process remains under state of control throughout commercial manufacturing. A system should be in place to detect the process variability and evaluating the unexpected deviations from the standard procedures. This stage involves monitoring and evaluation of critical process parameters, in process parameters and other information of the process in the routine manufacturing process, evaluation of the data will help in stating about the process performance by identifying the problems to take remedial actions for the improvement in the process. Continues monitoring at the level established during performance qualification until significant data is available to generate significant variability estimates.

Monitoring and evaluation of the process data should be an ongoing process related to the product quality, the data must include quality of the raw materials, in process quality and final product. Application of statistical process techniques, monitoring and data trending such as control charts for taking the critical control parameters is a good tool for effectively implementing the continued process verification. Stage 3 never ends until the product is discontinued.

Implementation of life cycle approach to the cleaning validation facilitates adoption of new technologies. Compare and trending the output comes and of an in process control to the specification limits, final output and quality of the product with statically by using different tools like process capability and process performance, sigma concept etc. This helps in continues improvement by implementing the proposed changes based upon the continuous improvement level of process understanding.

CONCLUSION: The approach to the cleaning validation in Pharmaceutical manufacturing has been changed and the minimal approach is no longer recommended. To maintain the product quality, previous product residue shall be cleaned thoroughly, otherwise it may be carried to the next product which results the failure or increase the impurity levels in the subsequent product. The cleaning methods, sampling methods, acceptance criteria, etc. should be done before the activity started.

The intention of this has been to define a comprehensive approach to the Validation of Cleaning procedures in Active Pharmaceutical Ingredient manufacturing facilities. The cleaning validation is not a single time activity; cleaning validation is continuous process consisting of three stages for starting and completion of cleaning validation with life cycle approach. Stage 1 (Process Design - Design and Development of the process with Quality by Design), Stage 2 (Process Qualification – Validation of cleaning process) and

Stage 3 (Continuous process verification- Improvement of process by trending the outputs).The life cycle approach for cleaning validation results the improvements by changing based on the process understanding gained during all three stages of cleaning validation. Effective cleaning validation is not a regulatory requirement and also a business development requirement by minimizing and preventing the failures of the cleaning process. The life cycle approach, comprising stage process design and development, reliable documentation of the cleaning validation, and ongoing monitoring and maintenance of the cleaning process, provides a structured approach for successful cleaning validation.

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