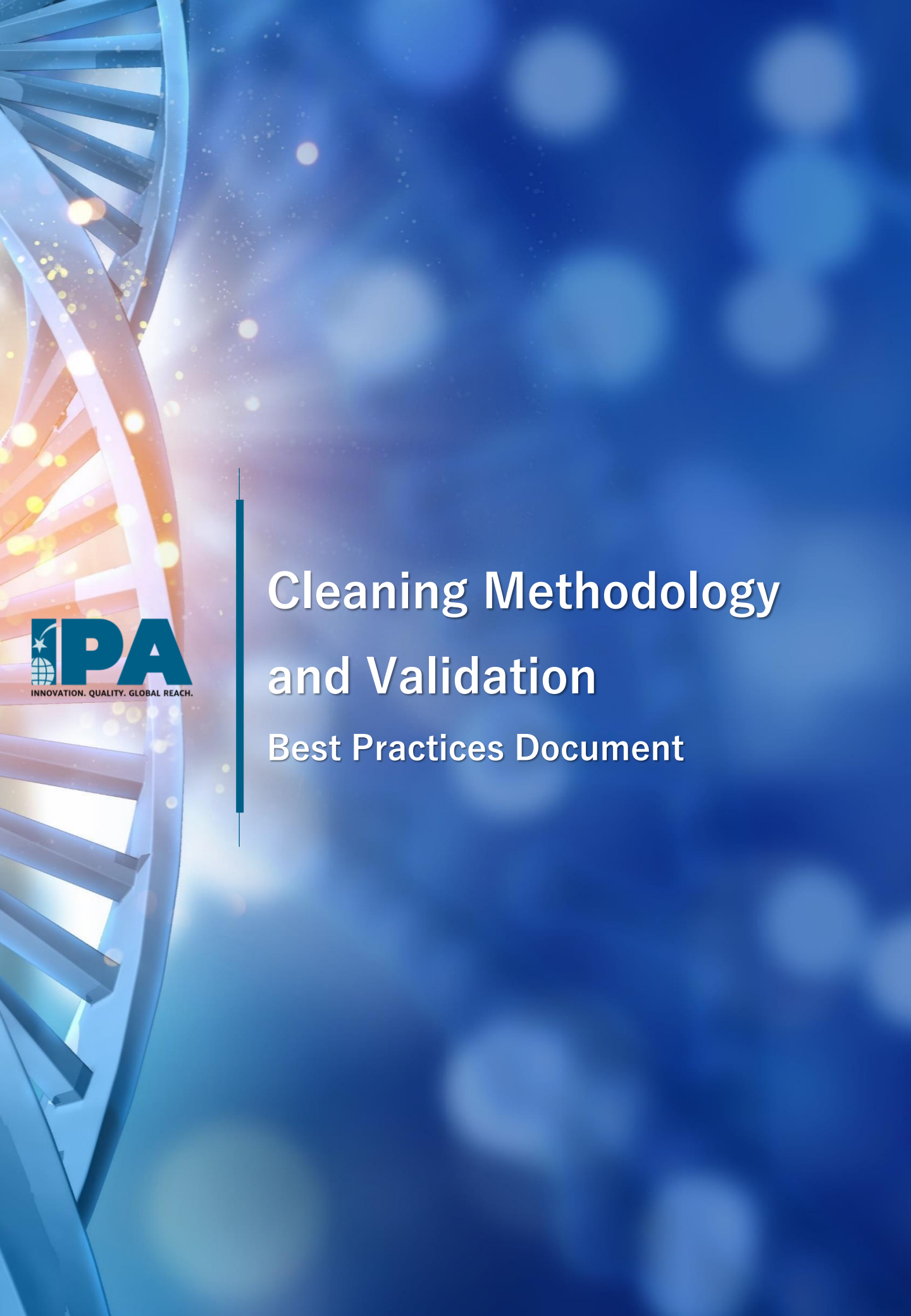
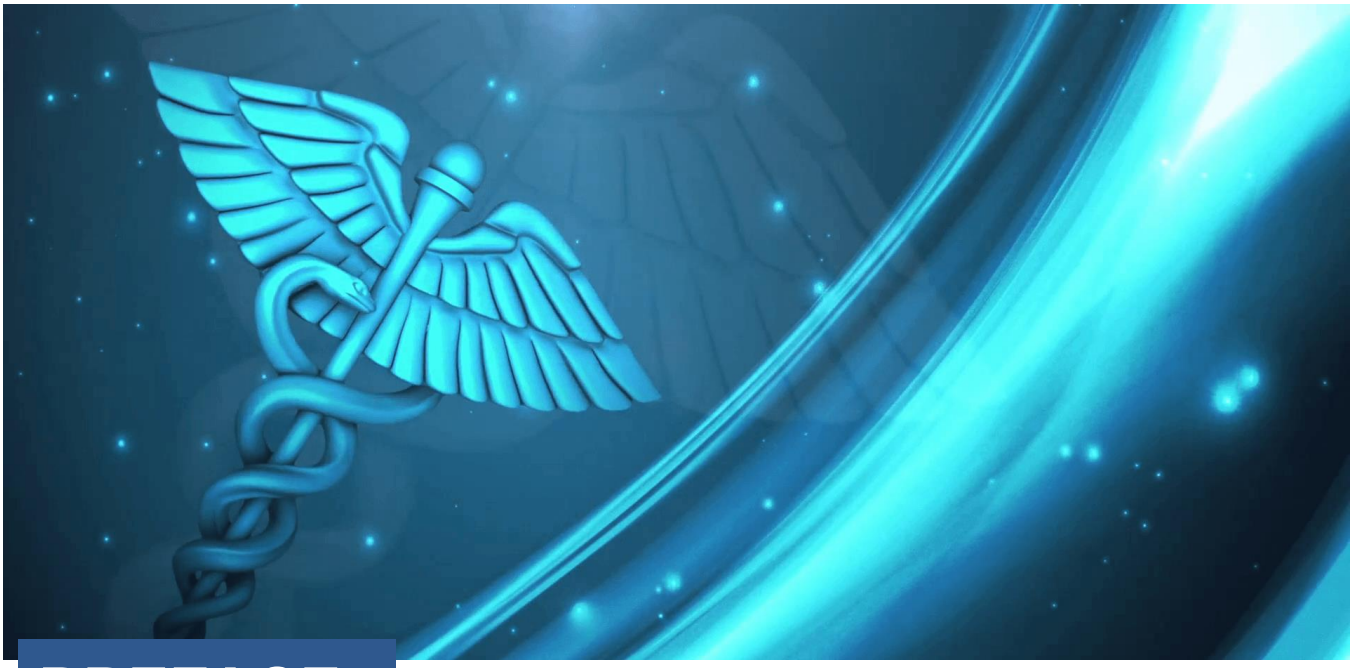


Cleaning Methodology and Validation

Best Practices Document

CONTENTS

CONTENTS



PREFACE

In April 2015, The IPA launched its Quality Forum (QF) to help Indian pharmaceutical manufacturers to achieve parity with global benchmarks in quality. The QF made a commitment to a multi-year journey to address key issues facing the industry and develop best practices.

The QF focused on several priority areas in the last four years, namely, Data Reliability, Best Practices & Metrics, Culture & Capability, Investigations, etc. It took upon itself the challenge of developing a comprehensive set of Best Practices Documents for several of these topics. In this document, we focus on best practices for Cleaning Methodology and Validation.

The six participating companies in the QF nominated senior managers to study the best practices and frame the guidelines. They are: Vipul Doshi (Cadila Healthcare) ; S V Gopalkrishnan (Cadila Healthcare); Sanjay Ghare (Cipla) ; Nilesh Hegu (Cipla) ; Krishna Mohan Mopidevi (Dr Reddy's); Gargi Sharma (Lupin); Navnath Pawar (Sun); and Tripti Gandhi (Torrent). The IPA wishes to acknowledge their concerted effort over the last 8 months. They shared current practices, benchmarked these with the existing regulatory guidance from the USFDA and other regulatory bodies such as UKMHRA, WHO, etc., developed a robust draft document and got it vetted by a leading subject matter expert and regulatory agencies. The IPA acknowledges their hard work and commitment to quality.

The IPA also wishes to acknowledge the CEOs of six member-companies who have committed their personal time, human resources and provided funding for this initiative.

This document will be hosted on the IPA website www.ipa-india.org to make it accessible to all manufacturers in India and abroad.

MUMBAI
MAY 2021

1 Introduction

1. Background

- Cleaning is the starting step for a manufacturing process. Validation is the process of providing documented evidence that a process consistently yields results which are reproducible. The cleaning validation demonstrates that the cleaning process provides a high degree of assurance that the cleaning shall consistently yield residue levels well below scientifically derived acceptance criteria.

- A well-defined cleaning procedure that is systematically developed and validated ensures that the risks of contamination is eliminated, thereby safeguarding patient safety and maintaining product quality.

- Of the several fundamental concepts of Good Manufacturing Practices prescribed through global regulatory agencies, the cleaning processes validation is the oldest GMP requirement, which is a well-adopted program by the pharmaceutical industry. With the growth and expansion in multiproduct manufacturing facilities that use common shared equipment for manufacturing, the cleaning validation becomes even more significant.

- Recently, cleaning validation has been one of the most evolving and debated topic and it involved several queries and concern with respect to practices. The purpose of this document is to provide Best Practices on the aspects of cleaning validation using the concepts mentioned from various global regulatory guidance including best practices followed among major Indian pharmaceuticals.

1.2 Purpose

- This IPA Best Practices Document: Cleaning Validation Lifecycle provides a hands-on approach to support the pharmaceutical industry in the development and establishment of a compliant cleaning program and its validation that meets or exceeds regulatory expectations.

- This Best Practices Document is not intended to interpret the GMP guidance provided by various regulatory agencies; however, it is intended to make an attempt and provide an approach towards setting up a cleaning and validation program that shall comply with requirements.

1.3 Scope

- This Best Practices Document covers the cleaning validation program and discusses the factors adopted for cleaning validation at the manufacturing facilities for pharmaceutical API and finished dosage forms. The cleaning validation program for biological facilities, vaccines, and medical devices facilities are out of scope of this Best Practices Document.

- It is assumed that an overall validation program already exists within an organization, and this encompasses validation philosophy for the facility, utilities, equipment and processes.

2 Guidance Plan

- This Best Practices Document is organized in such a way that it presents a major topic with a general section that applies to all segments of the pharmaceutical industry. Certain points may vary in a section depending on the specific product type, and an attempt has been made to cover those details in the section dealing with the specific product type.

2.1 Finished Dosage Form Manufacturers

- A drug product is manufactured by combining one or more raw materials, intended to produce a pharmaceutical dosage form such as oral solids/liquids (tablets, capsules, syrups, etc.), injections, ointments, inhalations and other forms.

- The finished products manufacturers often produce multiple products from shared common manufacturing equipment. The cleaning processes are largely manual and this poses a serious challenge during cleaning.

- The cleaning program of finished dosage form manufacturers is driven by an equipment specific approach, where the cleaning procedures are designed based on the equipment used; hence, typically, the facilities have one cleaning procedure for one equipment. Here, the cleaning procedures are designed and validated with the intent of getting rid of the residues of the molecules that are tough to clean. The same cleaning procedure is used after completion of manufacturing of all products.

2.2 Active Pharmaceutical Ingredient [API] Manufacturers

- The API or bulk pharmaceutical manufacturers produce the drug substances in large-scale manufacturing. These APIs are provided as input materials for the manufacturers of the finished dosage form. API manufacturing involves chemical synthesis that uses strong reagents and chemicals. The operations in these facilities are done in large closed equipment that is exposed to limited products.

- The cleaning processes of the equipment involved use chemicals and reagents, and as these are large and closed equipment, there is always a challenge in cleaning them.

- The cleaning procedure for API manufacturers is not equipment specific, but product specific. Here, for each equipment there could be multiple cleaning procedures which are defined based on requirement to remove the retained residues. As the APIs deal with reagents and chemicals, their removal is achieved by using the appropriate dissolving and extracting chemicals, with varied reaction time and temperatures. Hence the approach described above has been adopted.

- For both categories of facilities – finished dosage form and API manufacturers – it is very important to have a well-defined cleaning validation policy which will provide assurance that the contamination risks are eliminated.

3 Cleaning validation – Key Considerations

- Although the cleaning validation program is being followed by the industry, several differences in approaches are seen to be in use, and several observations are cited which point towards deficiencies in cleaning validation. Some of these are concerned with the absence of robust cleaning development process and ongoing monitoring. These weaknesses in a cleaning validation program can be attributed to complex and large multiproduct manufacturing facilities that have a varied product type and mix, coupled with not having a holistic evaluation of all elements that define cleaning efficiency.

- The key considerations section of this Best Practices Document is an attempt to provide the main points to be considered in any cleaning validations program. This section helps to identify the critical factors, determine the processes, equipment and products, develop scientific rationale and establish cleaning limits and methods.

- The key considerations for cleaning include the different type(s) of cleaning processes, equipment characteristics, product/process design, manufacturing parameters and analytical parameters. All these will directly affect the cleaning; however, based on the industry, the impact of these variables might vary.

3.1 Equipment Characteristics

- Pharmaceutical manufacturing equipment are typically designed to with suitable material of construction (MOC) that does not interact with the material of the manufacturing process and are also have smooth surfaces in order to facilitate proper cleaning. While designing the cleaning process, the following equipment characteristics are required to be evaluated.

    - Mixing tanks, tablet compression machines, capsule filling machines, centrifuges, granulators, filling lines, blenders, filters, fluidization equipment, coating equipment, batch process tanks, tubes, packing equipment, all need to be thoroughly cleaned.

    - The design of the equipment must be taken into consideration. By nature of its construction, some types of equipment will be more difficult to clean than others. Difficult to reach parts, dead legs and blind spots presents unique challenges for cleaning.

3.1.1 Ability to dismantle

- Equipment design must facilitate dismantling to the maximum extent possible so as to reach all the product contact surfaces while performing cleaning operations. The level of dismantling directly determines the efficiency of the cleaning process. This is very important for equipment that require manual cleaning. Dismantling of equipment is also important for certification of cleaning by visual inspection.

3.1.2 MOCs

- Material of construction of the equipment plays a vital role in cleaning. Equipment must be designed with the material of construction that ensures that the product contact surfaces are inert and does not react with the materials of the manufacturing and/or the cleaning process.

3.1.2.1 Product Contact Surfaces

- Typically, SS 316L is the preferred material of construction for all product contact parts. Also commonly seen product contact parts consist of food grade plastics, silicone material, etc. The product contact surfaces of equipment in use in API manufacturing facilities are typically made of SS surfaces or glass lined SS surfaces.

3.1.2.2 Other Surfaces (non-product contact)

- Other surfaces of equipment also are designed to facilitate cleaning and provide strength along with being non-corrosive to material. Typically, all surfaces are made of SS 316 or SS 304.

3.1.2.3 Dedicated and/or non-dedicated equipment

- Based on the product characteristics, the equipment might be required to be dedicated, or they can be shared across different products.

- It is important to understand if the equipment provides an opportunity for a thorough and extensive cleaning of all its components on the basis of its design.

- When satisfactory cleaning results cannot be achieved due to limitation in equipment design, the equipment should be modified or replaced. Similarly, if certain product contact parts are not feasible to dismantle and/or are difficult to clean because of their design factors, such as difficulty of access, presence of curved or grooved areas, hoses or tubing, etc., they need to be considered for dedication.

- Equipment parts, where preferential transfer may occur (filling needles, punches), should be considered for dedication.

- At times, the product and/or material being used in process renders the part to be used for a limited period, and continuing usage for many batches could lead to corrosion of the contact part; in such cases, dedication must also be considered for such parts of the equipment.

- Rationale for dedication of equipment should be available.

3.1.2.4 Age of Equipment

- The age of equipment needs special focus and attention. Aspects of equipment design, such as smoothness and finish to facilitate proper cleaning, are directly influenced by the age and usage of equipment. It is, therefore, necessary to review the equipment surfaces periodically for its finish and adequacy and its impact on cleaning efficiency.

3.2 Dedicated Facility

- Manufacturers should give due consideration for dedicating the facility with respect to product category/dosage forms being handled. Following are some examples:
    a. Cytotoxic products.
    b. Hormones.
    c. Beta lactam, Penicillin.
    d. Cephalosporins.
    e. Radiopharmaceuticals.
    f. Ectoparasiticides (e.g., substance for the treatment of lice).
    g. Highly active pharmaceutical ingredients (PDE equal to or less than 10 microgram).
- In such and similar cases, dedicated facility should be considered, if actual limits are not practical, achievable and verifiable.

3.2 Cleaning Types

- Pharmaceutical cleaning processes are designed and implemented in order to achieve efficient removal of residual material such as products, detergents and bioload remnants from equipment surfaces.

- Typically, any cleaning procedure and its efficiency are directly dependent upon the factors such as a) Time, b) Action, c) Chemistry, and d) Temperature. The diagram below represents the adhering forces that are likely to be removed by these factors, thereby rendering the surface clean.

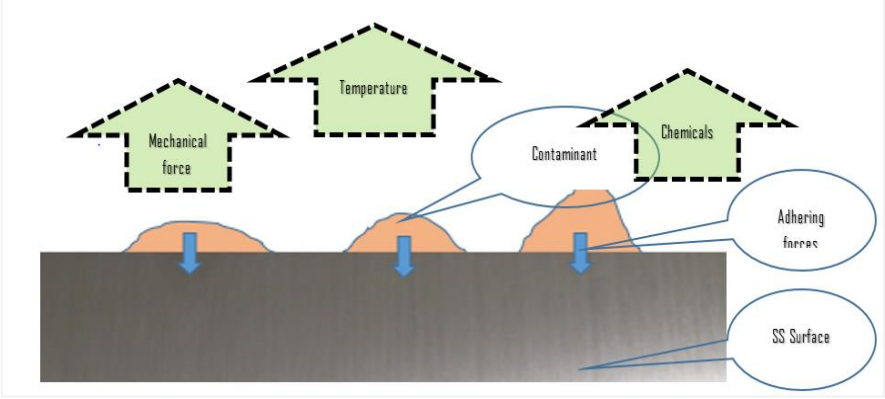


Figure 1
Representative drawing of SS surface with retained residue and factors needed to remove adherence

- The 'time' refers to the amount of time spent on a particular step, which would allow a contact for a certain period of time.

- 'Action' refers to the mechanism or movement adopted as part of cleaning, such as manually rubbing the surface with a pharmaceutical aid. The action provides a physical-mechanical action like impact and friction in order to reduce the affinity of the material to a surface, thereby dislodging any retained matter.

- ‘Chemistry’ indicates the importance of understanding the chemical properties of the product under cleaning with respect of its properties such as solubility, etc., and the selection of a suitable cleaning agent based on the same.

- ‘Temperature’ directly determines the cleaning efficiency. It is generally preferred to have the cleaning done at an elevated temperature for quicker removal of the retained material from a given equipment surface.

- These factors should be studied and optimized as part of the cleaning process development. Equipment of the pharmaceutical industry are equipped with possibilities for both ‘Manual’ and ‘Automated’ cleanings.

3.2.1 Manual cleaning

- Manual cleaning(s) are cleaning processes which are performed manually by trained personnel on equipment. These procedures are also called ‘Clean Out of Place’ (COP).

- Detailed instructions must be followed for any required disassembly and re-assembly of equipment if COP methods are used. Instructions should specify the:

    - Parts to be removed and any assembly aids used during this process.
    - Identification of all cleaning detergents and detailed instructions for their use. Usage instructions should include amounts, concentration, temperature, dwell time and application method.
    - Type of water: potable water or purified water.
    - Number of rinse steps required.
    - Drying and storage guidelines.

- Note: It is recommended that a failure mode evaluation be performed on the equipment, in order to identify the critical components (that has direct contact to the product surface/indirect product contact surfaces which are highly prone to contaminate the product, e.g., inlet duct) which would require the level of dismantling to do a thorough cleaning followed by visual check for cleanliness.

- Pharmaceutical aids such as non-fiber shredding scrubbers, nylon brush(es), sponges, scrapers, sprayers, wipes, etc., are used during the cleaning process.

- The manual cleaning processes are operator dependent and are prone to variations. Therefore, it is expected that the companies demonstrate the cleaning efficiency with various personnel through operator variability studies. Such an operator variability study should be part of the cleaning validation exercise wherein it is preferred to do the cleaning process validation runs with different operators involved in the cleaning process. It also requires supervision while performing the cleaning of equipment.

- Manual cleaning is not recommended for large equipment, where there are limitations to physical access and in situations where such large equipment are interconnected.

- It is also suggested that for multiproduct manufacturing facilities with manual cleaning, visual inspection along with periodic sample testing after cleaning is recommended as part of routine manufacturing even after completion of cleaning validations.

- In a multiproduct facility where high hazard active pharmaceutical ingredients are also manufactured in the shared facility, it is recommended that cleaning samples are analyzed after every product changeover in order to be assured of the effectiveness of the cleaning process.

3.2.2 Automated Cleaning

- Equipment with automated cleaning capabilities has built-in features to perform a cleaning process as per requirements. 'Cleaning In Place' (CIP) is generally used for large systems and components that cannot easily be dismantled. Spray systems, nozzles and immersion are a few examples of CIP operations.

- A CIP system in any equipment typically has the spray nozzles installed at strategic locations of the equipment. These nozzles are chosen based on contact surface of equipment to be cleaned, volume of the water/cleaning agent needed to be used and the water pressure required during cleaning. The spray nozzles are connected to a 'Wash In Place' (WIP) skids which is in turn connected to the water source.

- The CIP systems are automated systems operating on the basis of recipe. Cleaning recipes are developed by studying time of cleaning, pressure of water and number of cycles needed to clean the insoluble product. The CIP systems are qualified before starting to be used routinely. Spray coverage study and cleaning efficiency study are part of qualification of CIP systems. As these CIP systems are automated, they have the capability of producing the printout for every run cleaning cycle which can record details such as run time, flow rate/pressure, number of cycles, temperature of water, etc.

- Cleaning validation of CIP-based cleaning procedures is in same lines as a manual cleaning cycle, where the efficiency of the cleaning cycle is validated with an insoluble product candidate.

3.3 Product Characteristics

3.3.1 Drug Products

3.3.1.1 Cleanability

- Cleanability of a drug product, which is based on the physical properties of the formulation components, plays a vital role in the selection of a cleaning process. The assessment should look at physical properties including solubility in water and their composition percentage, in order to determine which formulations are considered the hardest to clean.

Material/Formulation Characteristics:

- Formulations characteristics directly impact the cleaning process/cleanability. For manufacturers of finished dosage form, the manufacturing process involves handling of dry material, semisolid material, and wet material. During the various phases, unique residue is created which will have different affinities to the product contact surface. Factors such as contact time, temperature and/or pressure involved in the stages add to degree of adherence of the material to the surface. During cleaning process development, it is required to study these factors including certain specific material characteristics such as color and smell at lab scale, and develop a robust cleaning process for commercial manufacturing.

3.3.1.2 Solubility

- To understand the cleanability, solubility of API and excipients used in the formulations should be considered.

- Typically, for manufacturers of finished products, cleaning procedures are equipment specific and are prepared targeting the insoluble components in the formulation.

- Solubility of the components in water and/or the organic solvents is required to be evaluated and documented. The difficult to solubilize components in water, and components which have the property of adhering to surfaces because of their sticky nature, pose major challenges to cleaning; hence, methods such as using a detergent and/or cleaning at elevated temperatures are generally adopted.

3.3.1.3 Dosage and Toxicology Limit

- Product dosage is one of the primary factors that are to be considered during setting of the cleaning validation limits. The recent EU update of “Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities” has provided a science-based setting of cleaning validation limits. In addition, the API manufacturers adopt the limits based on APIC guidelines for cleaning validation2.

- Limits based on toxicology use the Permitted Daily Exposure [PDE] values for Maximum Allowable Carry Over (MACO) limit calculation; this ensures that the previous product to the next product MACO is well below the safe limits.

- The expectation from the current regulatory guidelines is to select the MACO limit, which is lowest, obtained from the HBEL and dose-based calculation, and use the same as MACO limit during cleaning validations.

3.3.1.4 Hazardous and Non-hazardous Molecules

- Toxicology-based reviews provide guidance on the hazardous effects which come along with a drug such as carcinogenic effects, teratogenic effects, etc. In addition, it can also be concluded that the molecules with PDE values less than 10 ・g/day are considered to be hazardous and these are potent.

- This approach provides a clear risk-based categorization of the molecules within a multiproduct manufacturing facility as hazardous or non-hazardous, and, thus, provides an opportunity to take necessary additional technical and/or organizational control measures to avoid contamination.

3.3.1.5 Toxicological Considerations

- Toxicology limits (PDE/ADE) values determination is needed to be done by accredited toxicologists who have adequate qualification and experience. The EU guideline, "Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" provides clear requirements for toxicologists and considerations for review. It is expected that a procedure will be set up for reviewing these PDE/ADE monographs received from toxicologists for their adequacy, before accepting them for use in the cleaning validation program is put in place.

- Technical agreement should be in place if PDE value is contracted out or procured from an external expert. Assessment record should be available for legality (no conflict of interest), suitability and competence of the contract acceptor.

3.3.2 Use of Threshold of Toxicological Concern (TTC)

- When an ADE (PDE) is not available, such as for intermediates, degradation products, or compounds in early development, alternative approaches such as the threshold of toxicological concern (TTC) may be justified.

3.3.3 Drug Substances:

- The API manufacturers' cleaning procedures are product specific. They select cleaning procedure by studying the solubility, and extractability of the drug substance residues from the drug substance contact surface through its chemistry. Based on these studies, the cleaning procedure is created with time, temperature, pressure (vacuum) as variables with selected cleaning solvents.

4 Cleaning Validation Program

- Created by a team of Indian industry experts, this Best Practices Document is intended as a reference for the cleaning lifecycle model and a practical guide for applying the theory and concepts to help create compliant cleaning programs.

- It is aligned with the principles described in the several regulatory guidance documents available on cleaning validation.

- The validation of cleaning procedure consists of establishing the documented evidence that the procedure is effective and capable of removing the contaminants associated with previous products (actives, byproducts), residue of cleaning agents, potential microbial contaminants (TAMC, TYMC, Endotoxins) as applicable.x

4.1 Lifecycle Approach

- Cleaning validation traditionally emphasizes on demonstrating through a qualification program that the cleaning methods are effective, and work as intended. However, the current cleaning practices recognize that a better approach is to treat cleaning validation as a lifecycle, where the emphasis is shifted from performing cleaning qualifications to develop logical cleaning methods based on the product and type of equipment followed by qualification, together with ongoing cleaning verifications during use of a cleaning method.

- The cleaning validation lifecycle follows a similar model to process validation guidelines issued by FDA, EMA and other regulatory bodies.

- This lifecycle approach is more comprehensive than the traditional approach, as application of lifecycle ensures that the cleaning process are in the state of control and provides the logical progression of gaining knowledge for process improvements.

- Better knowledge of the cleaning process provides the tools necessary to assess the potential manufacturing cross-contamination risks, and helps to ensure a compliant and effective cleaning program.

- Note: Implementing a lifecycle approach will be challenging for legacy products where the development data may not be fully documented; however, a company can benefit from understanding the cleaning process parameters and design constraints when dealing with cleaning method changes and investigations of cleaning failures.

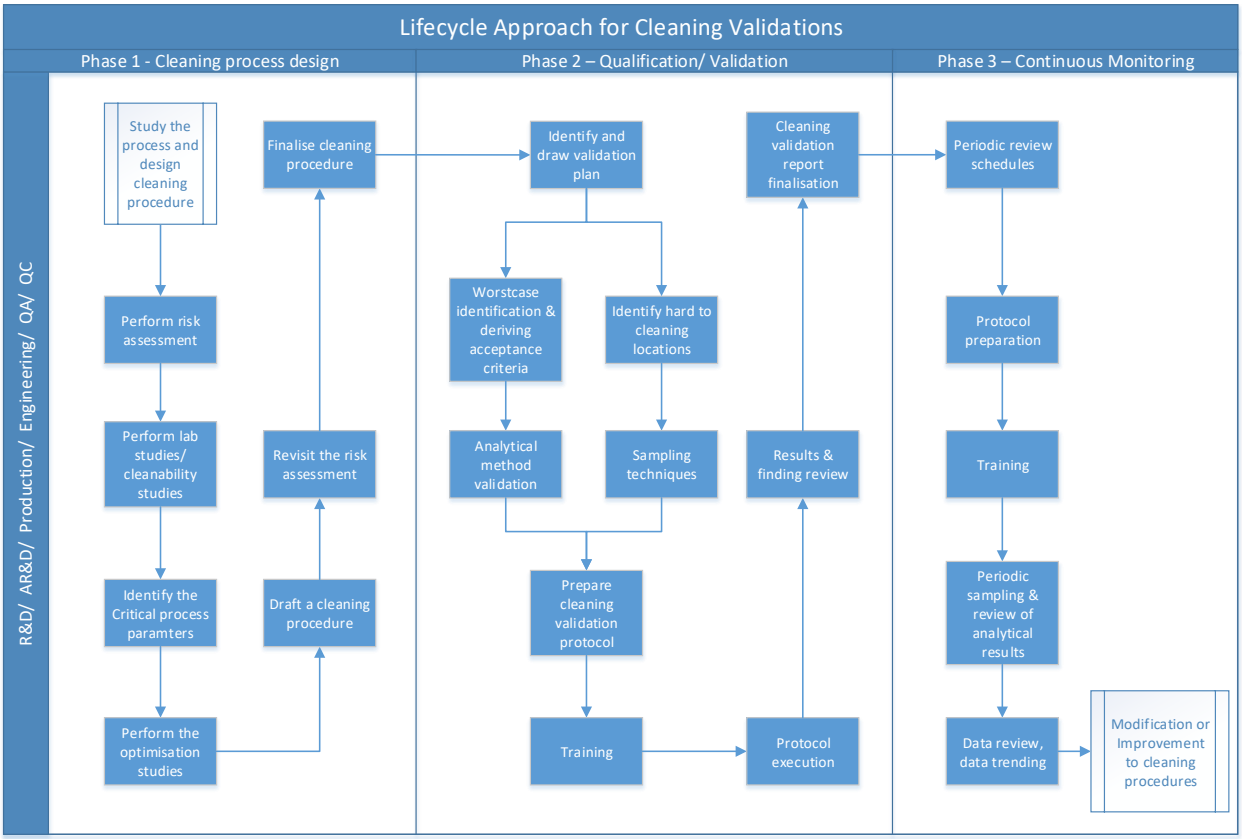


Figure 2
Life cycle approach for cleaning validation

4.1.1 Phase 1 - Cleaning Process Design

4.1.1.1 Procedure Design and Assessment:

- Cleaning procedures should be designed with adequate assessment to provide the expected assurance of consistency and effectiveness for the intended product(s) and equipment(s). The cleaning process requires design and development prior to implementation in a manufacturing plant in order to ensure the cleaning process and equipment are acceptable for use.

- Cleaning procedure design must be arrived by understanding the process, equipment design and other factors in collaboration with various cross functional team members such as R&D, Production, Engineering etc.

- The objectives of development should be a cleaning process, which is to be adopted, that is rugged enough to clean the worst case residue to levels below the cleaning limit, and that it should also be rugged enough so that in case new products and chemicals and their resulting residues are introduced into the facility, the existing cleaning process is still just as effective.

- During the process design stage, the cleaning process variables are set, criticality of parameters are assessed, and CIP/SIP cycle development (as applicable) and scale-up activities are completed. Laboratories studies are completed to support the development efforts in defining the cleaning process. This process can be documented in the validation strategy document or plan.

- The development of cleaning process involves important stages of elements, operation parameters, factors affecting the cleaning process as well as some specifics on cleaning process.

Important elements:

- **Residue characterization** : An evaluation should be performed to determine the characteristic of residues to be cleaned, keeping in mind solubility, concentration, cleanability, and holding time of residues on equipment surface.

- **Selection of cleaning agents** : This should be based on knowing what needs to be cleaned and the type of surface to be cleaned. Importantly, the cleaning agent selected should be compatible to the MOC of the surface to be cleaned. The cleaning agent to be used needs to be justified by laboratory studies taking into consideration the type and condition of residue/s to be cleaned.

- **Selection of cleaning process variables and justification of criticality** : Parameters that can directly impact on the cleaning process should be considered. For example: concentration of cleaning agent, time, temperature, volume, pressure, number of cleaning cycles, contact time/scrubbing time, need for initial rinse, duration of drying cycle, etc.

- **Review equipment design and inspection procedure** : This will include coverage, condition of equipment surfaces/surface finish/geometry of the surface, drainability, and level of lighting available for inspecting surfaces.

- **Determine residual limits and overall acceptance criteria** : The residual limits must not exceed the health based exposure limit. Arriving at the acceptance criteria is discussed in a later section of this Best Practices Document.

- **Selection of analytical methods** : The methods should be selective with a qualified Limits of Detection (LOD) which are below the residual limits and Limits of Quantification (LOQ) at the maximum equal to residual limit. If certain methods are not specific, other representative parameters may be selected, for example TOC.

- **Selection of microbial methods** : Microbial methods that have established the necessary recovery of organism should be used.

- **Defining sampling methods** : Appropriate sampling methods (direct sampling or indirect sampling) which have established the minimum expected recovery should be used.

- **Visual inspection** : The instructions to carry out visual inspections shall be clearly defined. Wherever required, visual inspection aids shall be used for examining the cleaned equipment surfaces. These visual inspection aids should include torches with high intensity illumination, GoPro cameras, etc.

- Procedures shall have adequate specificity to control parameters such as detergent/cleaning agent concentration, temperature, scrubbing time and manual cleaning actions, as well as a defined sequence of process steps. Adequate control also includes specification of detergent and cleaning tools (such as brushes or wipes).

4.1.1.2 Quality Risk Management

- After design of the cleaning procedure, a systematic quality risk assessment on the procedure before further studies will help in achieving robust controls that yield consistent results. Given below is a representative risk assessment for a cleaning procedure for a fluid bed drier.

Example 1: Key Components of Risk Assessment for FBD Cleaning Procedure

1. Risk Assessment tool selection: FMEA (Failure mode effect analysis) is a preferred tool for performing the quality risk assessment which will facilitate identification of the possible location of residue deposition, the level of dismantling required for equipment parts, the selection of tool required to clean, and the sequence of cleaning to be followed.

2. Identification of cross functional team (CFT): Manufacturing, Quality Assurance, Engineering and Technical Operation (also included are operators, immediate supervisors, maintenance engineers, IPQA team).

3. Equipment description: Purpose and functionality should be described.

4. Equipment operation and cleaning process: Manual or automatic cleaning should be specified.

5. Listing of such category of equipment should be mandatory at site, viz. FBD, equipment ID, make, design, use (function-drying, top/bottom spray, etc.).

6. Listing of major components and sub-parts should be available of the fluid bed dryer for contact and non-contact parts (including inlet air and exhaust air vents).

7. Schematic diagram of equipment should be available for easy understanding of cleaning process, air, material and water pathways, etc.

8. Supporting documents to perform the FMEA
    - ❖ Original equipment manufacturer (OEM) recommendations and review of equipment manuals.
    - ❖ Operation and cleaning procedures.
    - ❖ Photographs of fluid bed dryer components.
    - ❖ Comparison of fluid bed dryer components.
    - ❖ QMS data.
    - ❖ Interview documents.

9. Identification of
    - ❖ Potential failure modes which may lead to contamination/cross-contamination.
    - ❖ Areas which are difficult to visually inspect without dismantling.
    - ❖ Identification of powder adherence probabilities on high risk indirect product contact surfaces, including ducts, drains, lower plenum, etc.
    - ❖ Component-wise risk assessment to identify potential failure modes during cleaning (FMEA and recommendation for risk mitigation).
    - ❖ Risk management preparedness for conducting FMEA
    - ❖ Gemba Walk to understand the assembling and dismantling of equipment in view of cleaning and probability of deposition of product residues.
    - ❖ Interview with shop floor persons conducted to understand the existing cleaning process and identify action items for enhancement during FMEA assessment.

10. The OOS related to cleaning validation failure (historical review).

11. The deviation related to line clearance failures (historical review).

12. Retrospective review of QMS events (OOS/Deviations) – rating of probability of occurrence.

13. FMEA template:

Component	Sub-parts, if any	Photograph	Product Contact/Non-Contact	Failure Mode	Potential Effect(s) of Failure	Severity (S)	Rationale for Severity Rating	Potential Cause(s) of Failure	Probability of Occurrence (P)	Rationale for Probability Rating	Current Process Controls	How well one can detect the failure mode (D)	Rationale for Detection Rating	Risk Priority Number (RPN)	Risk Mitigation

Conclusion and Final Recommendations of FMEA Assessment:

- Precise instructions for dismantling and cleaning of subparts.
- Defining type of cleaning aids (scrubbers, brush, scraper, etc.).
- Defining aids to conduct visual cleanliness checks for components and parts of equipment (torch light, GoPro camera, etc.).
- Exploring engineering solutions for cleaning of large surfaces or ducts.

Example 1: FBD cleaning checklist (based on FMEA) and diagrams

4.1.1.3 Conducting Laboratory Studies

- Laboratory studies are recommended in order to best understand the characteristics of types of residues that could remain after manufacturing operations. The residue types can have various characteristics or conditions that may affect the chosen cleaning process.
- It is very important that the worst case conditions are tested during the laboratory evaluation. Cellulose based products become harder to clean as they dry, whereas denatured proteins and polymers are harder to clean if they are heated and baked onto the surface. As another example, wet granulation residues are difficult to clean when compared to dry granulation residues.

4.1.1.4 Identifying the Critical Process Parameters

- Similar to drug product/drug substance manufacturing, the critical process parameters (CPP) and critical quality attribute (CQA) are equally important for performing a cleaning program. It has to be noted that variation in CPPs can have a direct impact on the desired CQA. Hence, it is important to identify and establish the CPPs with development studies in order to achieve a consistent cleaning process. A typical list of CPPs and CQAs are shown below:

Critical Process Parameters (CPP)	Critical Quality Attributes (CQA)
Process Temperature	Product Residues
Process Pressure	Cleaning Agent residues
Process flow	Visual detection or limits
Process time	Microbiological residue limits
Cleaning agent concentration	Drying
Dirty and clean hold conditions	Conductivity or resistivity

- The development of the process should consider the number and complexity of issues surrounding the cleaning process and variety of facilities, products and equipment in use. Appropriate cleaning procedures must be developed for all product-contact equipment used in the production process. Consideration should also be given to non-contact parts into which product may migrate (e.g., equipment connecting ducts, seals, flanges, mixing shaft, fans of ovens, heating elements, etc.).

- Cleaning spectrum as listed in the table below can be used during the initial phases of defining a cleaning validation program or a new product cleaning process development. The cleaning spectrum helps the manufacturer to establish the factors which are critical for individual processes, thereby enabling the organization to set priorities, develop grouping philosophies and establish scientific rationales that will govern the cleaning program.

Cleaning Spectrum

Automated cleaning	Manual cleaning
Cleaning in place	Clean out of place
Dedicated equipment	Non-dedicated equipment
Indirect product contact surfaces	Product contact surfaces
Low risk location	High risk location
Minor equipment	Major equipment
Low risk drugs	High risk drugs
Highly characterized residue	Poorly characterized residue
Liquid formulations	Solid formulations
Easy to clean product	Difficult to clean product
Materials with smooth & non-porous surface	Porous materials
Single product facility	Multiple product facility
Non-campaign production	Campaign production

❖ Based on the above assessment the following different types of cleaning methods can be developed:

a. Cleaning in place
b. Clean out of place
c. Manual cleaning
d. Semi-automated cleaning
e. Automated cleaning
f. Solvent reflux cleaning
g. Placebo batch cleaning

❖ **Clean-in-place (CIP) systems** : This refers to an automated system, which can be a single pass or a re-circulatory system. It generally utilizes a spraying device to provide coverage and physical impingement on equipment surfaces. Examples are manufacturing tanks, blenders, fluid bed driers, reactors and fermentation tanks.

❖ **Clean-out-of-place (COP) systems** : Smaller equipment items or dismantled parts are transported to designated wash areas. These are generally done manually and hence a detailed procedure and appropriate training is required. It is important to ensure that the equipment is protected during transfer in common corridors.

❖ **Manual cleaning processes** : These are direct cleaning by trained operators using hand tools, cleaning aids and cleaning agents. Important cleaning parameters include volume of cleaning agent; volume of rinse water; temperature of wash and rinse solutions; sequence and duration of soaking wash and rinse steps; scrubbing actions; pressure of solutions; detergent concentration, etc.

❖ It is important to detail the instruction in cleaning SOP the extent of equipment disassembly to ensure the reproducibility of the cleaning process. Consistency of manual cleaning over the time is accomplished by operator training, adequate supervision and well defined and properly documented cleaning procedure.

❖ **Semi-automated processes** : This type of cleaning is an intermediate between a fully automated and a fully manual cleaning process, where some parts can be cleaned manually (by removing, dismantling, etc.) and the remaining through an automated cycle.

❖ **Automated processes** : This does not involves intervention (except perhaps to select a cycle and start/stop of the operation). Such a process is usually driven through a PLC or a computer program, where the control system regulates the cleaning cycle, addition of cleaning agent, temperature, time and other critical cleaning parameters. The validation of such a system is critical to the success of an automated cleaning process.

- **Solvent reflux cleaning** : This is appropriate for small molecule of API manufactured by organic synthesis, which involves boiling with a volatile solvent in a reactor vessel.

- **Placebo batches as cleaning method** : For highly viscous ointments and products or potent (hazardous) products, it may be feasible to use a placebo run as a method of cleaning equipment. The approach requires the use of a placebo that has no detrimental effect on the next manufactured product in the equipment. The disadvantages include the cost of cleaning and the difficulty in demonstrating the effectiveness of the process.

- For manual cleaning processes, consistency shall be controlled by adequate specification of actions in the written cleaning procedure, by training of operators and identifying important steps which needs supervision during the cleaning operation.

- Wherever manual cleaning is to be adopted, it is recommended that the cleaning process is developed by performing an FMEA on the equipment in order to identify the possible deposition of product residues. The outcome of this FMEA should help to determine the following:

a. Level of dismantling to be done
b. Identifying hard to clean surfaces
c. Logical steps of cleaning
d. Type of cleaning aids to be used
e. Important steps which needs supervision
f. Type of sampling aids
g. Type of visual inspection aids

- For automated cleaning processes, consistency shall be established by PLC control of cleaning parameters.

- Procedures may be written for specific equipment or for groups of equipment. Procedures may be specific to one manufactured product or may apply to a group of manufactured products on the same equipment and/or equipment group.

- Appropriate selection of analytical test method, sampling method, sampling locations, finalization of limits, etc., shall be done and draft SOPs with cleaning steps shall be attached with the cleaning verification protocol.

A typical cleaning process shall have the following steps:

Step	Function	Comments
Vacuum or pre-rinse	Removal of ready soluble and/or non-adhering residues.	Reduction in residue load prior to washing.
Washing with cleaning solution	Removal of soluble & dried residues. (Solubilizing residues by wetting with detergent, degradation or heat).	Primarily to remove residue or bioburden, often done at elevated temperatures. Use of detergents, alkali hydroxide or acids or combination of solvents or solvent mixture.
Rinse	Removal of suspended or solubilized residues and cleaning agents, as applicable.	May include series of rinses and final rinse with a higher grade of rinse solvent.
Dry	Removal of water and other solvent.	May be done by air or nitrogen flow or by heat.

4.1.2. Phase 2: Cleaning Process Qualification

- A typical cleaning process qualification should include the following prerequisites.

  - **Identifying worst case product/s** : This is discussed in subsequent sections.

  - **Qualifying equipment, reviewing utility readiness** : The equipment to be cleaned should be in the qualified state and, importantly from the cleaning prospective, the components (for example, Kärcher machine, spray jets, etc.) used for cleaning should also be verified for its proper operation. Utilities and corresponding distributing systems critical to the cleaning process should be in qualified state (for example, water, clean steam, gases, etc.).

  - **Cleaning SOPs** : The procedures defining cleaning steps and specific instructions to execute the cleaning process should be readily available and clearly documented.

  - **Qualifying cleaning agent suppliers** : Cleaning agent suppliers play an important role in supplying consistent material quality; hence documented evidence (supplier COA/Technical Agreement, etc.) on the composition of the cleaning agent is necessary. A certification on the composition of the cleaning agent and its consistent material quality should be available before execution of qualification.

  - **Analytical methods** : Validated analytical methods should be available.

- **Sampling Plan** : This shall include sampling locations, number of samples and the type of samples (swab or rinse). It is recommended that a pictorial representation of the actual equipment with identified sampling locations is readily available.

- **Justifying number of qualification runs** : The number of qualification runs should be risk based and supported by a documented rationale. The minimum recommended for qualification is three successful runs.

- **Creating a cleaning qualification protocol** : Approved cleaning qualification protocol requires details of predefined cleaning method, sampling plan, acceptance criteria and the number of runs.

- **Training to personnel** : The personnel involved (operators, laboratory analyst, samplers, supervisors and visual inspectors) in the cleaning function must have the necessary experience, and must be trained on SOPs related to cleaning and cleaning qualification protocol.

- On completion of above pre-requisites, the cleaning qualification protocol shall be executed and shall be concluded with a validation report.

- Knowledge gained during this phase may require the organization to go back to stage 1 for further development, or else, to proceed to stage 3, as part of the feedback and feedforward mechanism for lifecycle approach at all stages of cleaning validation.

4.1.2.1 Worst-case product selection

- Validation of cleaning processes should be based on a worst-case scenario including:

  i. challenge of the cleaning process to show that the challenge residue can be recovered in sufficient quantity, or demonstrate the log file of the removal to ensure that the cleaning process is indeed removing the residue to the required level; and

  ii. the use of reduced cleaning parameters such as overloading of contaminants, over-drying of equipment surfaces, minimal concentration of cleaning agents, and/or minimum contact time of detergents.

- The worst-case product is a combination of the product residue that is hardest to clean and the lowest cleaning limit for the products manufactured at a facility.

- Grouping is a strategy whereby manufactured products and/or equipment are considered together, and a formal protocol is performed on a representative from the group, which is usually the worst case among the products in the group.

- Grouping is also termed as matrixing, family approach or bracketing. The rationale is to generate optimum value from the cleaning validation task, based on the risk-based approach.

- The different approaches of Grouping are product families and choosing a worst-case product; by properties (e.g., solubility, potency, toxicity or formulation ingredients known to be difficult to clean)

- The hardest to clean formulations can be assessed in number of ways, as described below.

Approach 1: Worst-case based on cleanability

- One approach is to assess cleanability based on the nature of API and excipients by selecting the worst case using the least soluble product in the cleaning solution. Cleanability, in such a case, will be based on the physical properties of the formulation components.

- This assessment approach takes into account physical properties including solubility in water and their composition percentages in order to determine which formulations are considered the hardest to clean.

Example of formulation assessment (to derive the total insoluble material in Kg.)

Product Name	Ingredients	Solubility	Comp Qty. (kg.)	Insoluble Qty. (kg.)	Total Insoluble material (kg.) in batch
XXXXX Tablets USP YY mg	Active ingredient XXXXX	Insoluble *(slightly soluble)	56.9	56.9	235
	Anhydrous lactose	Soluble	375	NA	
	Dibasic calcium phosphate anhydrous	Insoluble	131.85	131.85	
	Povidone (k-30)	Soluble	25	NA	
	Purified water	Soluble	26	NA	
	Sodium starch glycolate	Insoluble	30	30	
	Magnesium stearate	Insoluble	6.25	6.25	
	Opadry white	Insoluble	10	10	
	Purified water	Soluble	115	NA	

- This assessment approach takes into account physical properties including solubility in water and their composition percentages in order to determine which formulations are considered the hardest to clean.

Example of worst-case approach:

S. No.	Product Name	API	Strength(MG)	Pharmacological Activity / Action	Type of Formulation	Batch size (Nos.)	BMR No.	LRDD (Nos)	Ratio of Batch size / LRDD (Nos)	API Solubility	PDE (mg/day)	Total Quantity of Insoluble components (Kg)
1	Aceclofenac Tablets 100 mg	Aceclofenac	100	Anti-inflammatory drug	Uncoated	110000	BMR/11	2	55000	Insoluble	0.1	21.074
2	Aciclovir Tablets 200 mg	Aciclovir	200	Antiviral drug (guanosine analogue)	Uncoated	150000	BMR/12	20	7500	Slightly Soluble	3.8	41.445
3	Alfuzosin Tablets 10 mg	Alfuzosin HCL	10	Treatment of prostatic hyperplasia (α1 receptor antagonist)	Uncoated	500000	BMR/13	1	500000	Freely Soluble	1.3	129
4	Ciprofloxacin Tablets 500 mg	Ciprofloxacin Hydrochlorid	500	Fluoroquinolone antibiotic	Coated	125000	BMR/14	3	41667	Sparingly soluble	1	23.312
5	Donepezil Tablets 10 mg	Donepezil Hydrochloride	10	Treatment of Alzhemer's disease	Coated	125000	BMR/15	1	125000	Soluble	0.25	20.32
6	Glimepiride Tablets 4 mg	Glimepiride	4	Treatment of Type-2 Diabetes melitus (Anti diabetic ag	Uncoated	100000	BMR/16	2	50000	Insoluble	0.05	3.04
7	Lansoprazole Tablets 30 mg	Lansoprazole	30	Antacid (Proton-pump inhibitor), Used for Ulcers	Uncoated	125000	BMR/17	6	20833	Insoluble	1.25	69.56
8	Losartan Potassium Tablets 50 mg	Losartan potassium	50	Anti-hypertensive (angiotensin II receptor antagonist)	Coated	500000	BMR/18	2	250000	Soluble	0.05	0.05
9	Sertraline capsules 50 mg	Sertraline HCL	50	Antidepressant (the selective serotonin reuptake inhibitor)	Capsule	500000	BMR/19	4	125000	Slightly soluble	0.83	38.747
10	Dutasteride and Tamsulosin HCL Capsules 0.5mg	Dutasteride	0.5	5-α reductase inhibitor	Capsule	350000	BMR/20	1	350000	Insoluble	0.01	325.433
		Tamsulosin	0.4	Used in benign prostatic hyperplasia	Capsule	350000	BMR/21	1	350000	Slightly Soluble	0.0133	325.433
11	Valacyclovir tablets 500mg	Valacyclovir	500	Antiviral drug	Coated Tablet	400000	BMR/22	3	133333	Freely soluble	33.3	53.68
12	Paroxetine HCL tablets 20 mg	Paroxetine Hydrochloride	20	Antidepressant (selective serotonin reuptake inhibitor)	Coated Table	1400000	BMR/23	3	466667	Slightly Soluble	0.116	502.74

Evaluation for Worst Case Previous Product

- Based on the Technical evaluation i.e. Total quantity of Insoluble components below are the stage wise worst cases identified for ABC facility:

1. Granulation , Compression and Coating stage:- Paroxetine HCL Tablets 20 mg (BMR No. BMR/23) is identified as worst case for ABC facility with total Insoluble components of 502.74 kg for granulation, compression and coating stage . Hence this product shall be considered as worst case for above mentioned manufacturing stages of ABC facility.

2. Capsule Filling Stage :- The product Dutasteride and Tamsulosin HCL Capsules 0.5mg/0.4mg (BMR No. BMR/23) is identified as worst case for Capsule Filling stage of ABC facility with total insoluble component of 325.433 kg .

Evaluation for Next Product for Calculation

- Lowest ratio of “Batch size/ LRDD" is identified as 7500 for product Aciclovir Tablets 200 mg. Hence, this value shall be considered for MACO calculation of product under cleaning validation/verification study for ABC facility.

Approach 2: Based on risk prioritization (RPN)

- Worst-case selection can be based on following factors using risk assessment/rating:

a. Hardest to clean: experience from production. (This is subjective and should be supported by scientific rationale, documented experience on how difficult a molecule is to clean out, and interviews with operators and supervisors. Three categories of experience may be used: 1 = Easy; 2 = Moderate; 3 = Difficult).

b. Solubility in used solvent. (Here the grouping is based on molecule solubility in solvent using solubility categories, as illustrated below).

Group	Description	Approximate quantities of solvent by volume for 1 part of solute by weight
1	❖ Very soluble ❖ Freely soluble	❖ less than 1 part ❖ from 1 to 10 parts
2	❖ Soluble	❖ from 10 to 30 parts
3	❖ Sparingly soluble ❖ Slightly soluble	❖ from 30 to 100 parts ❖ from 100 to 1 000 parts
4	❖ Very slightly soluble	❖ from 1 000 to 10 000 parts
5	❖ Insoluble	❖ more than 10 000 parts

c. Lowest Acceptable Daily Exposure or Permitted Daily Exposure (ADE/PDE defines limits at which a patient may be exposed every day for a lifetime with acceptable risks related to adverse health effects).

Group	Include dose intervals (smallest therapeutic dose)
1	>250 µg
2	> 50 to 250 µg
3	> 5 to 50 µg
4	> 1 to 5 µg
5	Up to 1 µg

If ADE/PDE data are not available, other pharmacological dose, OEL or toxicity data (LD50) may be used.

d. Lowest therapeutic dose (or toxicity data LD50). (Therapeutic doses are typically applicable for oral and/or parenteral data).

Group	ADE / PDE
1	>100 mg
2	> 10 to 100 mg
3	> 1 to 10 mg
4	> 0.01 to 1 mg
5	Up to 0.01 mg

- Risk rating can be done using above criteria to arrive at the worst-case molecule.

Example of Approach 2:

- If the hardest to clean product can be cleaned down to the level of product with lowest acceptance criteria, then all products with a common cleaning process are considered validated.

Risk Factor	SRDD (mg)	PDE (mg/day)	Solubility in water/ cleaning solvent	Cleanability
5	Up to 1	Up to 0.01	Insoluble	Difficult
4	> 1 to 5	> 0.01 to 1.0	Very slightly soluble	------
3	> 5 to 50	> 1.0 to 10.0	Slightly/sparingly soluble	Moderate
2	> 50 to 250	> 10.0 to 100.0	Soluble	------
1	> 250	> 100.0	Freely/very soluble	Easy

Facility : ABC

Document no. : XXX (V-0)

Product Name	Active pharmaceutical ingredient (API)	API Solubility in water (Risk Factor)	PDE (mg/day)	SRDD (mg) (Risk Factor)	Cleanability (Risk Factor)	Total RPN
Glipizide and Metformin HCL Tablets 2.5mg/250mg	Glipizide	Insoluble (5)	1 (4)	2.5 (4)	Easy (1)	80
Glipizide and Metformin HCL Tablets 2.5mg/250mg	Metformin HCL	Freely Soluble (1)	62.5 (2)	500 (1)	Easy (1)	2
Indomethacin Capsules 25mg	Indomethacin	Insoluble (5)	0.2 (4)	25 (3)	Easy (1)	60
Indomethacin Capsules 50mg	Indomethacin	Insoluble (5)	0.2 (4)	25 (3)	Easy (1)	60
Metformin Hydrochoride Tablets 500 mg	Metformin HCL	Freely Soluble (1)	62.5 (2)	500 (1)	Moderate (3)	6
Amlodipine Besylate Tablets 10 mg	Amlodipine Besylate	Slightly Soluble (3)	2.5 (3)	2.5 (4)	Moderate (3)	108
Common pellets Esomeprazole magnesium 20 mg & 40 mg	Esomeprazole magnesium dihydrate	Slightly Soluble (3)	0.05 (4)	2.5 (4)	Moderate (3)	144
Base granuls Esomeprazole magnesium for 20 mg & 40 mg	Esomeprazole magnesium dihydrate	Slightly Soluble (3)	0.05 (4)	2.5 (4)	Moderate (3)	144
Meloxicam Tablets 15 mg	Meloxicam	Insoluble (5)	3.33 (3)	7.5 (3)	Moderate (3)	135
Pravastatin Sodium Tablets 10 mg	Pravastatin sodium	Soluble (2)	30.0 (2)	10 (3)	Moderate (3)	36
Clindamycin Hydrochloride Capsules 300 mg	Clindamycin Hydrochloride	Freely Soluble (1)	50.0 (2)	450 (1)	Moderate (3)	6
Ezetimibe Tablets 10 mg	Ezetimibe	Insoluble (5)	25.0 (2)	10 (3)	Moderate (3)	90
Lansoprazole Tablets 15 mg	Lansoprazole	Insoluble (5)	1.25 (3)	15 (3)	Moderate (3)	135
Lansoprazole Tablets 30 mg	Lansoprazole	Insoluble (5)	1.25 (3)	1.25 (3)	Moderate (3)	135
Glipizide Tablets 2.5 mg	Glipizide	Insoluble (5)	1 (4)	2.5 (2)	Moderate (3)	240
Ezetimibe Tablets 10 mg	Ezetimibe	Insoluble (5)	25 (2)	10 (3)	Moderate (3)	90

Evaluation for Worst Case Previous Product

- Highest Total RPN is 240 for product "Glipizide Tablets 2.5 mg" . Thus, this product become selected worst case previous products for cleaning validation study of ABC facility

Deriving worst cases based on:

Product grouping

- Products may be grouped if they are cleaned by the same cleaning process. If a product in the group requires a more aggressive cleaning process, that product becomes the worst-case product in that group.

- Grouping of products can be done by type and the worst case may be determined by performing risk assessment, considering the solubility, ADE/PDE levels and cleanability. Specific dosage forms, viz. oral solids (general category), can be one group; oral solids (potent category) can be another group; similarly aerosols; nasals; transdermals; topical preparations; animal products can be other groups. The grouping should be logical and practical in order to achieve the end goal, which is meeting the acceptance criteria of the cleaning procedures by using the analytical methods supporting the residue limit acceptable. Grouping of facilities at the same campus sharing same/similar equipment train and same harmonized cleaning procedures can be considered. Dedicated facilities are preferred for products with highly hazardous actives or pharmacologically sensitive actives/molecules.

- For Vitamins Manufacturing: The drug products containing vitamins as API shall be out of scope of cleaning validation, considering that these products are used as dietary supplement and not likely to have any adverse effect on pharmacological action of the subsequent product manufactured and on patient safety. However, the same cleaning philosophy for changeovers and the validated cleaning procedure shall be followed after product manufacturing.

- One option for product grouping is to use a surrogate worst-case product. In this situation, the worst-case product is an artificially constructed product (and may not be a commercial product), designed to be more difficult to handle than routinely manufactured products. The construction of such a product may include ingredients which are easily available and at low cost. Ingredients of such formulations should be insoluble (including polymers having low limit of detection). Another ingredient may be micro susceptible which can be formulated in wet granulation. This product should represent the worst-case scenario for cleanability, possibility of detection using HPLC/UPLC method for faster detection, and should have low disposal cost. One rationale for this approach is to maintain the continuity of the worst-case product; another rationale is to minimize situations in which new worst- case products are added.

- The acceptance criteria for the worst-case product are generally the most stringent acceptance criteria of all the products in a group.

- Successful cleaning validation of the representative product means that the cleaning of the other products in that group is also validated.

- Based on the risk assessment (addressing both quality risks and business risks), one approach is to perform a single confirmatory run on every product during product introduction. Also based on the risk assessment, another approach is to perform qualification protocol runs on all parameters, i.e worst-case products, the most difficult to clean product and the product with lowest limits.

Equipment grouping

- Establishing through scientific rationale that equipment sharing same design and construction can be grouped for validation purposes may reduce the total number of validation runs necessary to demonstrate consistency of the cleaning process.

- Identical/similar equipment can be grouped. However, due attention should be paid to considerations of complexity and different sizes; the two extremes of the largest and the smallest sizes should be considered. Confirmatory runs on other equipment which is not worst-case can be done.

- A specific case of equipment grouping involves minor equipment, such as utensils, small parts, and smaller equipment. In such cases, it may be appropriate to evaluate a cleaning procedure for such parts and to validate the cleaning process using equipment grouping. The grouping of parts involves selection of worst cases based on the complexity, size and functionality.

- Equipment with the same operating principle and design, the same cleaning procedure, and the same product contact surface areas and sizes, but with different working volumes, can be grouped together (e.g., rotary compression machine, mechanical sifters, oscillating granulators, vacuum transfer system). In such cases, determination of the worst-case equipment in the group may be based on criteria such as largest working volume.

- Equipment with the same operating principle/design and the same manual cleaning procedure, but with different product contact surface areas and sizes that vary by not more than a factor of 5:1, can be grouped together (e.g., large and small tablet presses). In such cases, the equipment are considered equivalent, and any single equipment or a combination of multiple equipment may be used as the representative equipment for the validation protocol runs.

- Equipment with the same operating principle/design and the same CIP cleaning procedure, but with different product contact surface areas and sizes that vary by not more than a factor of 5:1, can be grouped together, provided that the CIP spray devices in each case provide 100% coverage in a coverage qualification test, and further provided that the contact times of cleaning solutions with the equipment surfaces are equivalent. In such cases, the equipment are considered equivalent, and any single equipment or a combination of multiple equipment may be used as the representative equipment for the validation protocol runs.

Example of equipment grouping

Equipment: Fluid Bed Dryer (FBD)			FBD group: 500 – 800 L		Cleaning SOP/Checklist No: SOP-ABC-XX
Sr. No	Product Name	BMR No.	Version	Total Insoluble components (kg)	FBD ID
1	Atenolol Tablet 100 mg	BMR/2	1	642.5	MC/432
2	Paracetamol Tablets 750 mg	BMR/9	2	148.68	MC/432
3	Carvedilol Tablets 25 mg	BMR/22	0	88.95	MC/432
4	LEVOFLOXACIN TABLETS 500 MG	BMR/38	4	164.756	MC/219
5	Tamsulosin HCL capsules 0.4 mg	BMR/63	1	1623.2	MC/121
6	Valacyclovir tablets 500mg	BMR/67	0	53.68	MC/219
7	Metformin HCl Tablet 1000 mg	BMR/81	1	148.75	MC/432
8	Atorvastatin Calcium Tablets 80 mg	BMR/86	0	418.605	MC/219
9	Donepezil HCL tablets 10 mg	BMR/92	1	60.96	MC/219
10	Losartan Potassium 100mg and Hydrochlorothiazide 25 mg tablets	BMR/94	4	73.53	MC/219

Evaluation for Worst Case Previous Product

- Highest Total RPN is 240 for product "Glipizide Tablets 2.5 mg" . Thus, this product become selected worst case previous products for cleaning validation study of ABC facility

Combining Product and Equipment Grouping

- The most common cleaning validation at a site involves a combination of product grouping and equipment grouping. This means that, for a group of products that is manufactured on a group of equipment, the worst case (or representative) product in the product group will be utilized for the validation protocol utilizing the worst case or representative equipment for that equipment group.

4.1.2.2 Sampling technique

- The sampling plan should be defined that describes the sampling location (description/schematic diagram and photograph), number of samples and types of samples (microbiological, chemical API, cleaning agent, placebo, blank sample, etc.). It is important to take into account the sequence of sampling; e.g., in general, the microbial sampling should be taken first followed by others on a particular piece of equipment.

- Justification should be provided for the selection of the appropriate verification technique on a case by case basis. A combination of the two methods is generally the most desirable. For all methods, the sampling points should be fixed in a manner such that the true contamination of the equipment will be reflected.

- The selection of sampling locations should be based on a risk assessment. Sampling should be done by qualified and trained samplers. Proper sampling is of the utmost importance, as it is the tool for evaluating cleaning effectiveness by establishing the level of residues present.

- Swab sampling is the preferred method to be used. Rinse samples should be taken for areas which are inaccessible for collection of swabs for sampling.

- Appropriate sampling procedures, swab material and sampling techniques should be selected and used to collect swab and rinse samples. The detail should be clearly described in procedures and protocols.

- The number of swabs, location of swabbing, swab area, rinse sample volume and the manner in which the samples are collected should be scientifically justified.

- Swab and rinse sample analytical methods should be validated. Recovery studies for swab and rinse sampling should be performed.

- Where microbiological sampling is carried out, the microbiological method should also be validated.

- The manner in which collected samples are stored (if required) and prepared for analysis should be appropriate, described in detail and included in the cleaning validation.

Swab sampling (direct surface sampling)

- Swab sampling of the direct surface is designed to test small sections of the equipment surface for the presence of residues. Samples should be taken from all main equipment items, and, since swab sampling does not cover the entire equipment surface area, justification should be provided for the choice of the area for swabbing.

- Swab sampling involves manually moving a wetted swab across a defined surface area of the equipment in a defined pattern in order to remove residues by solubility and/or physical action from the surface onto the swab head.

- Typically, a small area of the cleaned equipment is swabbed with a material according to a pre-defined method, i.e., swab material, solvent and technique. The swab sample can then be extracted and examined using a suitable analytical method.

- Swab wiping should be unidirectional at a time. Parallel stokes should be employed to cover the entire swab area.

- **Swabbing from irregular surfaces** : If swabbing is not possible on a flat surface due to the equipment design, an equivalent area should be swabbed. If the swab area available is smaller than the defined and required swab area, then the complete area should be swabbed

Rationale for selection of swab sampling method and when to perform rinse sampling

- Swab sampling is the preferred method as swabbing is a direct surface sampling method, while rinsing is an indirect method.

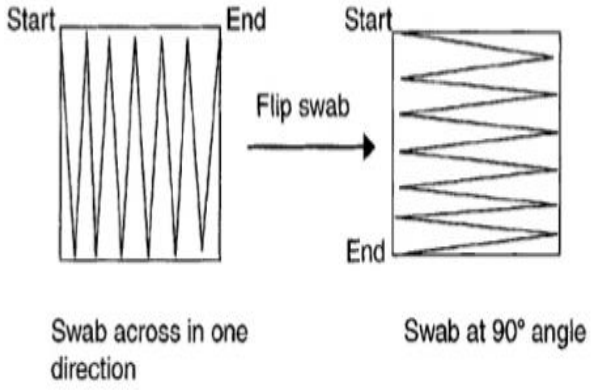
- By swab sampling, areas that are hardest to clean and which are reasonably accessible can be evaluated. Additionally, residues that are insoluble can be sampled by physical removal.

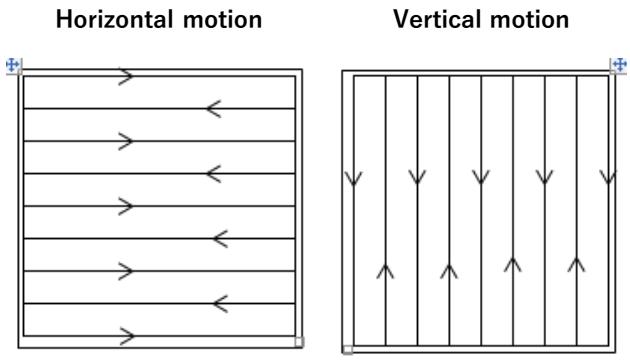
- However, rinse sampling involves sampling equipment by rinsing solvent over all relevant equipment surfaces to remove residues, which are then measured in the rinse solvent.

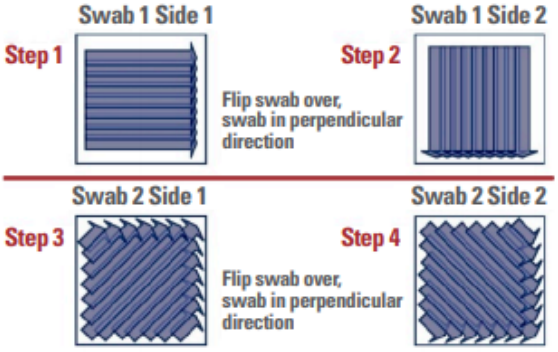
- Rinsing is more suitable for pipes, longer tubes and larger tanks with connecting valves – in short, places that are not easily reached.

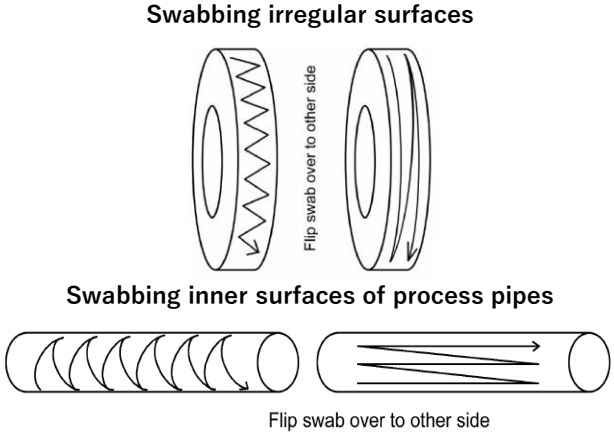
- The use of swabs is critical in determining the contamination level found around imperfections in production equipment, such as rough surfaces, weld points, cavities or in places where general rinsing will not easily contact the equipment surface.

- Refer picture below:









- Stainless steel/Teflon /PVC templates should be used for swabbing on defined surface area. In general, the swab sampling area is 4 square inches or 16 square inches. Selection of swabbing area should be defined in procedure and protocols for surface area determination.

- Eyeball method: This method should be used for remote surfaces which are not reachable or for surfaces with complex geometry. In such cases, the use of swab at one end of an extension pole may be used, by trained personnel.

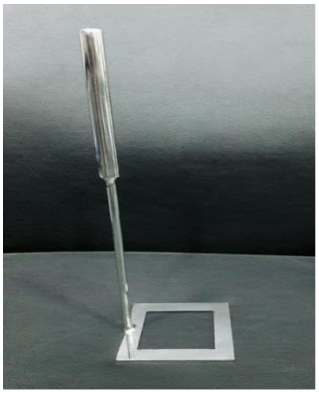
- Swab sampling should be taken within the groove of two different materials (of construction parts come together).

- While sampling using templates, care should be taken to clean the templates with water or wipe with Isopropyl Alcohol.

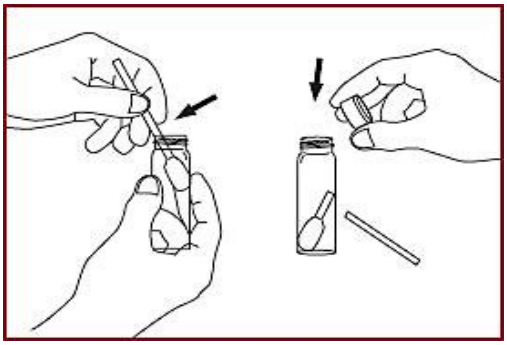
Template Examples








Teflon/PTFE/SS



Type of swab

- Swab and swab materials should be
    - Convenient and easy to use.
    - Able to take residue from coupon and equipment surface.
    - Able to release residues into solution.
    - Not cause any interference with residue.
    - Made of material that do not shed particles (wooden sticks must not be used).
- It is important to determine the type of sampling material used and its impact on the test data, since the sampling material may interfere with the test. For example, the adhesive used in swabs has been found to interfere with the analysis of samples. Therefore, early in the validation program, it is important to assure that the sampling medium and solvent (used for extraction from the medium) are satisfactory and can be readily used.
- Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used. Typical contact surfaces are stainless steel, rubber, Teflon, glass, silicon, PFA, Halar, plastic, Tefzel, acrylic, neoprene, EPDM, Hypalon, PP plate, etc.
- Advantages of direct sampling are that areas that are hardest to clean and which are reasonably accessible can be evaluated, leading to establishing a level of contamination or residue for a given surface area. Additionally, residues that are "dried out" or are insoluble can be sampled by physical removal.
- The size of swab head depends on the swab area and level of the residue on the surface. Swab stick should be long enough so that the risk of touching the swab head is low.
- The swabs are often fibrous materials (knitted, woven or non-woven) attached to a plastic handle, which are applied to the sampled surface. The selection of swabs or wipes to be used requires an evaluation of swab properties, extractables or shedding properties. Recovery of residues from surface also depends on the size and shape of swab head or wipe, as well as the properties (such as flexibility and length) of the swab handle.
- In addition to having minimal analytical interferences, high quality cleaning validation swabs must allow for high recovery rates. Recovery rates are a function of swabbing method as well as material absorption and residue-releasing properties of the swab.

- In addition to having minimal analytical interferences, high quality cleaning validation swabs must allow for high recovery rates. Recovery rates are a function of swabbing method as well as material absorption and residue-releasing properties of the swab.

- In most cases, the swabs and wipes are wetted with a solvent prior to sampling the surface. The solvent selected should assist in dissolving the residue and also be compatible with the method. The extraction solvent may be same or different from the solvent that is used for wetting of the swab.

- Swabbing pattern, wetting solvent, and type of swab used during sampling should be similar to those used during recovery study.

- It is recommended to wipe the swabbed surface with 70% Isopropyl Alcohol after removing the swab samples from different locations and visually inspect for cleanliness of equipment surface.

- Cleaning validation employing these analytical methods is a complex activity requiring a careful selection of the procedure and materials involved. Establishing a capable method begins with the selection of the swab.

Number of swabs

- A single swab will provide adequate recovery and require minimal amount of extraction solvent to maximize the LOD for residues; this also simplifies the swab process. A larger area more often requires multiple or larger swabs to achieve a sufficient RF, but the larger volume of extraction solvent required offsets some of the sensitivity advantage gained from increased sample size.

    - It is recommended to use one swab for sampling for one location.

    - One swab should provide consistent, adequate recovery for most residues from most MOCs.

    - Multiple swabs may be used if one swab does not recover an acceptable level of residue. It should also cover other factors for low recovery - swab solvent, swab technique, and extraction solvent. If multiple swabs are used, these should be combined in order to obtain one residue level for the swab location.

4.1.2.3 Identification of sampling sites

- Selection of swab location should be based on the following:

    - Material of construction (MOC).

    - Design of the equipment from the point of view of reachability.

- ❖ Difficulty of inspection.
- ❖ Areas where residue build up is possible.
- ❖ Locations that are first to accumulate residue, and last to lose residue during cleaning.
- ❖ Porous surface.
- ❖ From microbiological perspective, areas which have higher potential for microbial growth (e.g., areas with stagnant water, areas that are open to environment, etc.).
- ❖ Number of locations should reflect the size and complexity of equipment and provide representative picture of cleanliness of cleaned equipment.

❖ Typical worst case swab location rationale has been discussed for Fluid Bed Dryer

Representation Type 1

Equipment	Swab location	Hard to clean	Product contact	MOC	Residue build up	Seam	Pinch point	Hard to reach	Contamination risk	Irregular shape	Can retain water	Liquid air interface	Occluded location
Fluid Bed Dryer/WC	Product Container		√	√									
	Agitator rake at the bottom of the product container	√	√	√			√	√					
	Sampling port located at the product container	√	√	√	√					√			
	Filter plate	√	√	√						√			
	Inner surface of Wurster column		√					√		√			
	Entire surface of the nozzle tip		√	√	√					√		√	

Representation Type 2

Equipment Name: Fluid Bed Processor/Dryer/Equipment

Sampling location	ID. No.	Rationale for swab selection of sampling location
For Active Pharmaceutical Ingredient		
Inside the bowl wall	FC1	Representative functional location of inner bowl surface coming in direct contact with API.
Gasket (bowl)	FC2	Representative materials of construction (rubber or silicone).
Inside the retarding chamber	FC3	Representative functional location of inner surface of retarding chamber coming in direct contact with API.
Inside the retarding chamber (top)	FC3- T	Representative functional location of inner top surface of retarding chamber coming in direct contact with API.
Between screen and wall	FC4	Difficult to clean location, such as joint between two different parts, i.e., bowl wall and mesh which is prone to retain product remnants.
View port (glass and SS)	FC5	Representative materials of construction for view glass and difficult to cleaning location such as joint between two different parts.
Charging port	FC6	Location likely to produce non-uniform contamination on batch due to shape of the port, i.e., hollow cylindrical shape.
Sampling port	FC7	Location likely to produce non-uniform contamination on batch due to shape of the port, i.e., hollow cylindrical shape.
Discharge port with valve of bowl	FC8	Location likely to produce non-uniform contamination on batch due to shape of the port, i.e., hollow cylindrical shape.
Gasket ring (duct flap)	FC9	Representative materials of construction (rubber or silicone).
Near the drain port	FC10	Representative functional location of plenum as the API drains from this location during cleaning.
Inside the duct of plenum	FC11	Difficult to clean, as equipment part has hollow cylindrical shape with possibility of retaining product remnants that can enter the location while processing or cleaning, even though location is not in direct product contact.
Inside the duct after flap	FC12	Difficult to clean, as equipment part has hollow cylindrical shape with possibility of retaining product remnants that can enter the location while processing or cleaning, even though location is not in direct product contact.
Flap Surface (back side)	FC13	Difficult to clean location, as equipment part is not directly exposed to water jet during cleaning; thus there is possibility of retaining product remnants that can enter the location while processing or cleaning, even though location is not in direct product contact.
Drug loading nozzle/gun (inside surface)	FC14	Location is not visible and not directly exposed to water jet with high probability of retaining API remnants leading to non-uniform contamination of next batch.

Sampling location	ID. No.	Rationale for swab selection of sampling location
For cleaning agent		
Inside the bowl wall	FD1	Representative functional location of inner bowl surface.
Gasket (bowl)	FD2	Representative materials of construction (rubber or silicone).
Inside the retarding chamber	FD3	Representative functional location of inner surface of retarding chamber.
Inside the retarding chamber (top)	FD3- T	Representative functional location of inner top surface of retarding chamber.
Between screen and wall	FD4	Difficult to clean location as joint between two different parts, i.e. bowl wall and mesh, is prone to retain the product remnants.
View port (glass and SS)	FD5	Representative materials of construction for view glass, and difficult to cleaning location since this is a joint between two different parts.
Discharge port with valve of bowl	FD8	Location likely to produce non-uniform contamination on batch due to shape of the port, i.e. hollow cylindrical shape.
Gasket ring (duct flap)	FD9	Representative materials of construction (rubber or silicone).
Inside the duct of plenum	FD11	Difficult to clean as equipment part has hollow cylindrical shape with possibility of retaining product remnants that can enter the location while processing or cleaning, even though location is not in direct product contact.
Flap Surface (Back side)	FD13	Difficult to clean location as equipment part is not directly exposed to water jet during cleaning; thus, there is the possibility of retaining product remnants that can enter the location while processing or cleaning, even though location is not in direct product contact.
For Microbial		
Inside the bowl wall	FM1	Representative functional location of inner bowl surface.
Inside the retarding chamber	FM2	Representative functional location of inner surface of retarding chamber.
Inside the duct of plenum	FM3	Difficult to clean as equipment part has hollow cylindrical shape with possibility of retaining product remnants that can enter the location while processing or cleaning, even though location is not in direct product contact.

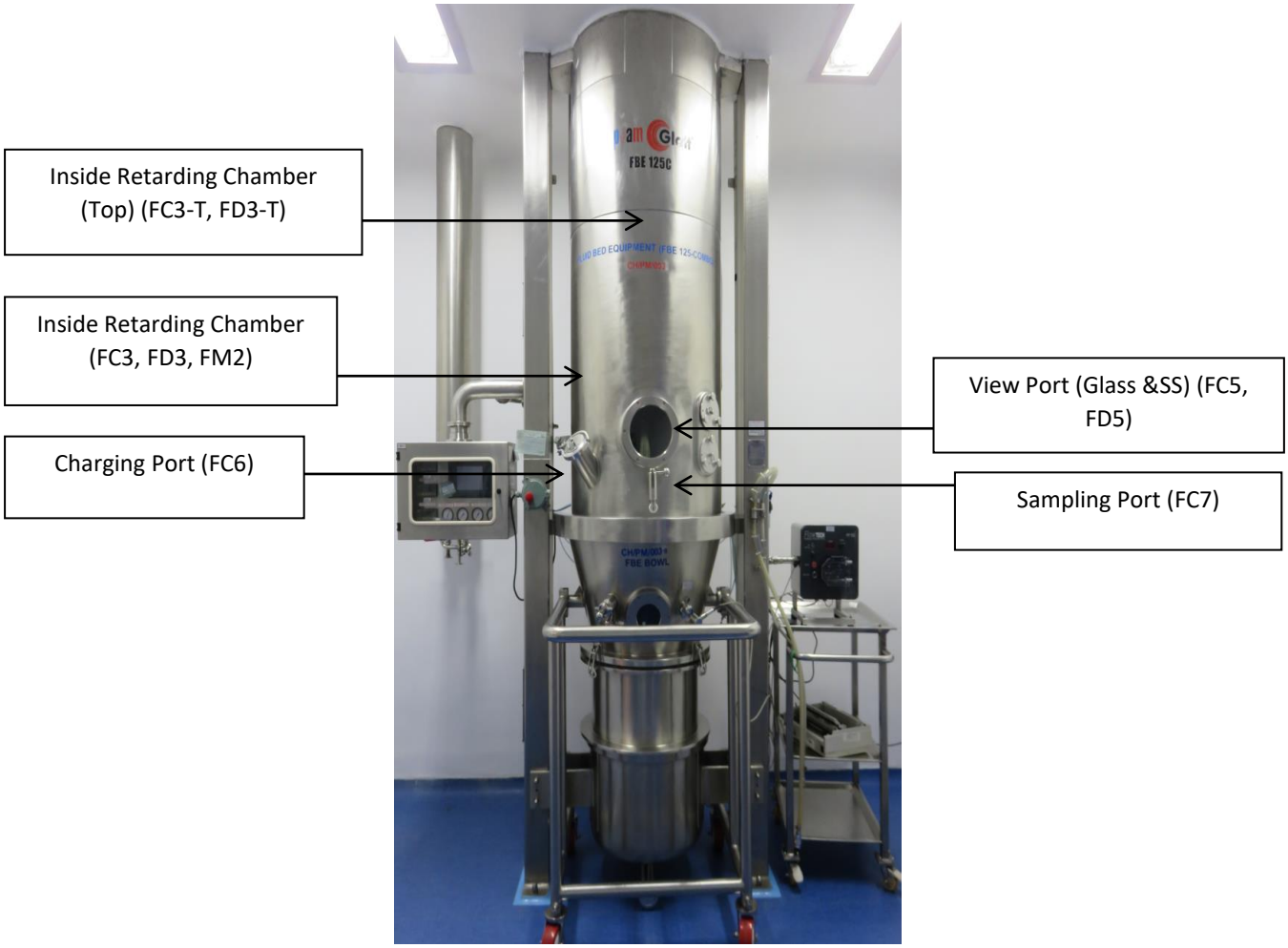
RATIONALE

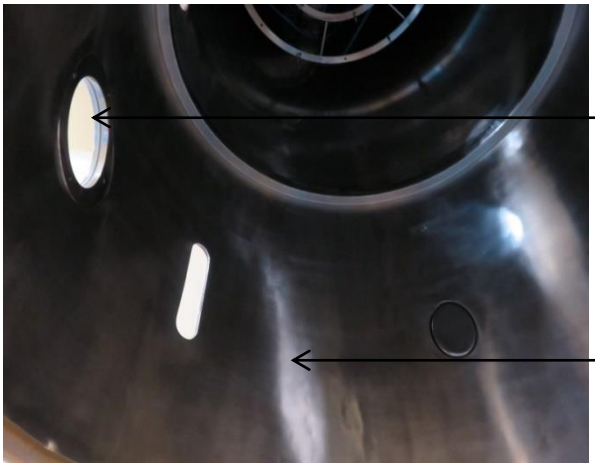
- The rationale for the each sampling location is based on the four following criteria
    - Most difficult to clean locations.
    - Locations likely to produce non-uniform contamination of next batch.
    - Representative functional locations.
    - Representative materials of construction.

Rationale for Selection of Swab sampling location for Cleaning agent and Micro

- The locations selected for cleaning agent should be adjacent to the swabbed area. It will give representation of remaining residue of cleaning agent on the equipment surface after cleaning. The number of swabbing location may be less than the number of swab samples for active residue. This may be due to the smaller surface area available for sampling, and severity of API is more as compared to cleaning agent. As a rule, priority is always given to API.

Swab location: Pictorial Presentation of Swab Location of actual Equipment (Representation Type 2)





Inside Retarding Chamber (Top) (FC3-T, FD3-T)

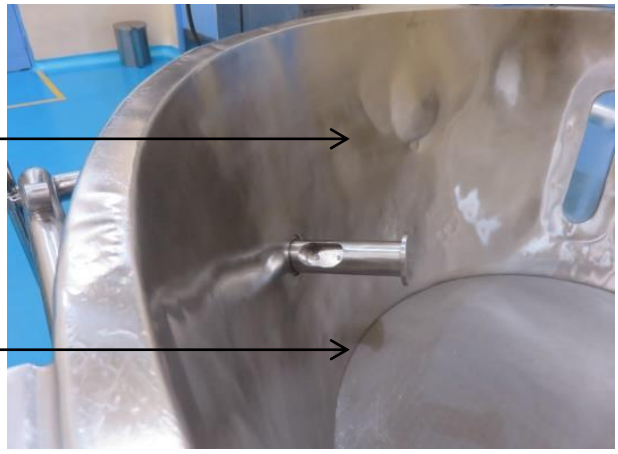
Inside Retarding Chamber (FC3, FD3, FM2)

Inside Retarding Chamber (FC3, FD3, FM2)

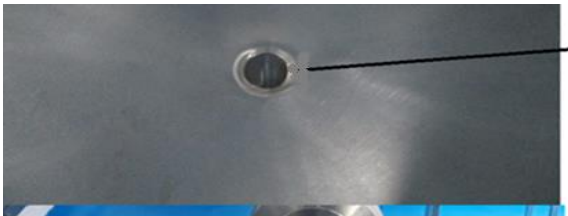
Sampling Port (FC7)

Discharge Port with valve of Bowl (FC8, FD8)

Inside Bowl Wall
(FC1, FD1, FM1)



Between Screen and Wall
(FC4, FD4)



Near Drain Port (FC10)

Inside duct of Plenum (FC11, FD11, FM3)

Inside duct after Flap (FC12)

Flap Surface (Back Side) (FC13, FD13)

Gasket ring (Duct Flap) (FC9, FD9)

Inside surface of Drug Loading Nozzle/Gun (FC14)

Note: In case of two different swabs at same location, subsequent swabbing should be performed at adjacent location from previous swab area as indicated.

Swab Order

- The order in which multiple swab samples are taken is important to prevent cross-sample contamination. The recommended order is:

- Microbial (bioburden)→ Chemical API → Chemical detergent

  - Bioburden samples (as it is most sensitive to contamination).

  - TOC samples (before using organic solvents to avoid contamination).

  - Samples using organic solvents to be taken at the end.

Examples of Swabs

Swab type examples	
Texwipe Cleaning Validation Series swabs all use polyester fibers in their head material which offers wide solvent compatibility. This compatibility is essential for recovering the residue off the surface and depositing it into the preselected diluent for testing.	Nylon membrane filter (Pall Gelman Science/ Pall Life Science/Membrane disk filters)
	

Qualification of swab sampler doing sampling

- The people doing the swabbing have always been considered to be a major factor in variability of swab recovery data; hence swabbing technique should be emphasized during training and swab qualification. It should be ensured that all personnel use the accepted technique. If other equipment (e.g., extension pole) are used for sampling certain pieces of equipment, it is imperative that personnel are trained and qualified.

- Relevant personnel should be qualified with at least triplicate recovery at one level of a chosen residue (preferably 100%) using the swab, solvent and surface area used for sampling. Acceptance criteria should be established. For example, the average recovery of the uncorrected three recoveries are within +/- 10% of the established RF with a variability of </= 15% RSD.

- Periodic swab sampler requalification should be considered as part of stage 3 (Continued Cleaning Verifications).

Rinse sampling (Indirect Sampling)

- This is an indirect sampling method as any remaining surface residue is not taken directly from the surface. It is performed by collecting an aliquot of either the final rinse or a separate sampling rinse from a piece of equipment or equipment train after cleaning. The absence of residue in rinse infers absence of residue on actual surface.

- It is important to note that for the purposes of cleaning validation, rinse samples alone would not be acceptable, unless a direct measurement of the residue or contaminant has been made.

- Rinse samples allow sampling of a large surface area and of inaccessible systems or ones that cannot be routinely disassembled. However, consideration should be given to the fact that the residue or contaminant may be insoluble or may be physically occluded in the equipment.

- A direct measurement of the residue or contaminant in the relevant solvent should be made when rinse samples are used, in order to validate the cleaning process.

Requirements of rinse sampling

1. Rinse solvent should dissolve the target residue.

2. Rinse solvent should reach all product contact surface areas.

3. Surfaces should be rinsed long enough to ensure complete coverage of equipment surface and sufficient removal of target residue.

- Rinse sample is usually taken from the last rinse of the cleaning cycle or a separate additional rinse post-cleaning sample rinse. Quantity of rinse volume should be mentioned in protocol or procedures.

Requirements of rinse solvent

- This should have high solubility of product to be removed. If post-clean rinse is used, it should have an equal or higher solubility as the final rinse for target residue.
- This should not degrade the product.
- This should be compatible with equipment.
- This should not interfere with subsequent residue analysis.
- This should not contaminate subsequent batch.

- Note: Hazardous solvents (benzene, ethylene dichloride, etc.) and recycled solvents prone to generation of nitrosamine impurities should not be selected as rinse solution or cleaning agents.

Sampling for microbiological testing (bioburden)

- Various sampling techniques in order to confirm microbial cleanliness include using sterile swabs/contact plates from the surface samples and rinse samples. Cleaning agent should be checked to identify their level of bioburden, if any.

- Swab for microbial testing should be taken from locations at site that is difficult to clean and is usually from a different surface location from chemical swabs. Swab for microbial testing are less in number compared to chemical swabs, usually one or two depending on size and complexity of equipment. Sampling should be done from dry surface and at ambient temperature. Micro samples should be collected before chemical swab sample.

- Swab collecting frame must be sanitized with 70% Isopropyl Alcohol (IPA) before sampling for microbial residue.

Swab type for microbial evaluation

- Sterile HIMEDIA cotton swabs or COPAN make swabs can be used. Negative control (blank) swabs should be sent.

Alternate sampling methods

- The direct sampling method using swabs or indirect sampling method using rinse is a traditional approach for sampling. The sample collected is subjected to testing using a validated analytical method.

- Recent trends in cleaning validation sampling techniques involve sampling using innovative technologies and techniques to develop and validate a methodology based on an in situ hand-held Process Analytical Technology (PAT) to verify manufacturing equipment cleanliness. This advancement in sampling helps eliminate swabbing and associated offline laboratory testing. A few examples of the novel techniques are:

- Specular Reflectance Mid Infrared (Mid-IR) spectroscopy, used to detect and quantify surface residue. It is expected that this analytical technique will allow the elimination or reduction of the number of swabs, and subsequent offline analytical testing required during cleaning verification of manufacturing equipment in the pharmaceutical and biopharmaceutical industry. This study was focused on the development and validation of a Mid-IR based calibration model. The results indicate that surface residue of 0.19 μg cm$-$2 for a specific molecule is detectable using the specular reflectance Mid-IR technique. 11

- TOC enables manufacturers to deploy Process Analytical Technology (PAT) for a cleaning validation program. Using at line or online technology for cleaning validation greatly increases the efficiencies of a monitoring program. Not only are data and equipment released in real time, but time spent on sampling, analysis, and human error in investigations, are greatly reduced using PAT applications. Furthermore, TOC can aid in optimization of the cleaning process itself. Using TOC data, the amount of water, detergents, and time may be reduced based on process profiling capabilities of online cleaning validation deployment. Finally, as mentioned in the previous point, obtaining data every four seconds with Turbo mode can significantly aid in process optimization.

- Indirect testing such as conductivity and TOC testing may be of some value for routine monitoring once a cleaning process has been validated. This could be applicable to reactors or centrifuge and piping between such large equipment since these can be sampled only using rinse solution samples.

4.1.2.4 Acceptance criteria

- The limits established in cleaning validation should be justified. The determination of cleaning limits and acceptance criteria are crucial elements of a cleaning validation program. A limit is typically an actual numerical value and is one of the acceptance criteria of a cleaning validation protocol. Limit and acceptance criteria should be:

    - Practical (actual cleaning situation to be validated).

    - Verifiable (by a qualified analytical procedure).

    - Achievable (by cleaning process for the product and by analytical methodology available for target residue).

    - Scientific sound (rationale for limit chosen).

Acceptance criteria should include:

1. Visual observation.

2. Chemical residue of API.

3. Chemical residue of detergent (if applicable)

4. Microbial and endotoxins.

- Criteria such as Maximum Safe Carryover (MSC)/Maximum Allowable Carryover (MACO) and Maximum Safe Surface Residue (MSSR) values should be calculated. Calculations and data should be available and should comply with data integrity principles. The calculation should include values of PDE, maximum daily dose, batch size and total shared equipment surface areas.

- Individual swab/rinse sample results should comply with calculated swab/rinse limit as per respective cleaning validation/verification protocol.

- The total carryover of the equipment train should be less than the calculated MACO of that particular equipment train.

- Validated spreadsheet should be used for calculations, and calculations should be documented and reviewed by a second competent person.

- Executed cleaning record/checklist and equipment cleaning cycle printouts (original or true copy) should be attached with cleaning verification/validation report, or maintained separately till retention time of verification/validation report.

- Raw data for surface area calculation of each equipment should be available.

MACO Calculations (active residue, cleaning agent, microbial test)

Calculation of limits for actives for swab and rinse sampling

- The residue limit for a drug active should be established based on the calculations below. The following calculations involve first determination of the most stringent of the three criteria (PDE-based and 0.001 dose-based), then calculation of the total carryover per batch (L2), then the limit per surface area (L3), then the limit per swab (L4a) and finally the limit in a rinse sample (L4c). The limit for swab sampling (L4a) is an amount (mcg) per swab, while the limit for a rinse solution (L4c) is a concentration limit (mcg/g, or ppm) in the rinse solution.

- The most stringent of the three criterion is done by comparing L1 (limit as concentration in next product) for each of the three criteria as given below.

L1 for PDE-based criterion is calculated as given below.

$$L1 = \frac{(PDE)}{(LRDD) \times (UW)}$$

Where,

L1 = concentration allowed to next batch, in mcg/g (or ppm)

PDE = Permitted Daily Exposure of the active in the cleaned product, in micrograms (mcg)

LRDD = the maximum daily dose of the next manufactured drug product, in units

UW = mass of one unit for the next manufactured product (in grams)

L1 for the 0.001 dose-based criterion is calculated as given below.

$$L1 = \frac{(SRDD) \times 1000}{(SF) \times (LRDD) \times (UW)}$$

Where,

L1 = concentration allowed to next batch, in mcg/g (or ppm)

SRDD = smallest recommended daily dose of the drug active in the cleaned product, in milligrams (mg)

SF = safety factor (typically 1,000 for all routes of administration)

LRDD = the maximum daily dose of the next manufactured drug product, in units

UW = mass of one unit for the next manufactured product (in grams)

- Note: In this calculation, 1000 given in the numerator is to convert from mg to mcg. Based on the smallest (most stringent) of the L1 values calculated above, that criterion is used for the subsequent calculation for L2.

- Cleaned product is defined as: "As used for cleaning validation/verification protocols, the product on which cleaning process is performed in the protocol. This is the product for which limits for active is calculated."

Calculation of L2 (total carryover per batch)

- Based on the smallest (most stringent) of the three L1 values calculated, that criterion (PDE-based & dose-based) is used for the subsequent calculation for L2.

For PDE-based criterion, the L2 limit is calculated as given below.

$$L2 = \frac{(PDE) \times (Batch\ size)}{(LRDD) \times 1000}$$

Where,

L2 = total carryover amount allowed to next batch, in milligrams (mg)

PDE = Permitted Daily Exposure of the active in the cleaned product, in micrograms (mcg)

Batch size = minimum batch size of next manufactured product, in units

LRDD = the maximum daily dose of the next manufactured drug product, in units

- Note: In this calculation, 1000 given in the denominator is to convert from mcg to mg. The batch size and LRDD should be from the same product.

For dose-based criterion, the L2 limit is calculated as given below.

$$L2 = \frac{(SRDD) \times (Batch\ size)}{(SF) \times (LRDD)}$$

Where,

L2 = total carryover amount allowed to next batch, in milligrams (mg)

SRDD = smallest recommended daily dose of the drug active in the cleaned product, in milligrams (mg)

Batch size = minimum batch size of next manufactured product, in units

SF = safety factor (typically 1,000 for all routes of administration)

LRDD = the maximum daily dose of the next manufactured drug product, in units

❖ Note: The SRDD dose is the smallest dose for the active for that product therapeutic category. The batch size and LRDD should be from the same product

Calculation of limit per surface area (L3):

$$L3 = \frac{(L2) \times 1000}{(Surface\ Area)}$$

Where,

L3 = limit per surface area, in mcg/in2

L2 = the lowest L2 value from previous section in milligrams (mg)

Surface area = total combined surface area of the product contact parts, in inch2

❖ Note: In this calculation, 1000 given in the numerator is to convert from mg to mcg.

Calculation of limit per swab (L4a):

$$L4a = L3 \times (Swab\ Area)$$

Where,

L4a = limit per swab sample, in micrograms/swab (mcg/swab)

L3 = limit calculated in previous section, mcg/in2

Swab area = area swabbed, in inch2

Calculation of limit in rinse sample (L4c):

$$L4c = \frac{L3 \times (Rinse\ Area)}{(Rinse\ Amount)}$$

Where,

L4c = limit in rinse sample, in micrograms/gram (mcg/g)

L3 = limit calculated in previous section in mcg/in2

Rinse area = area rinsed, in inch2

Rinse amount = Amount (in grams) of liquid use for final rinse of equipment

Calculation of limits for detergents in swab and rinse sampling

❖ The residue limit for a detergent should be established based on the calculations below. These calculations are based on the most stringent of a LD50-based criterion and a 100 ppm in the next product criterion. PDE-based calculations are not used because PDE values for detergents are not commonly available. The following calculations involve first determination of the most stringent of the two criteria (LD50-based and 100 ppm-based), then calculation of the total carryover per batch (L2), then the limit per surface area (L3), then the limit per swab (L4a) and finally the limit in a rinse sample (L4c). The limit for swab sampling (L4a) is an amount (mcg) per swab, while the limit for a rinse solution (L4c) is a concentration limit (mcg/g, or ppm) in the rinse solution.

Calculation of L1 (limit allowed to next batch)

❖ The most stringent of the two criterion is done by comparing L1 (limit as concentration in next product) for each of the two criteria as given below.

L1 for the LD50-based criterion is calculated as below.

$$L1 = \frac{(LD50) \times BW \times 1000}{(CF) \times (LRDD) \times (UW)}$$

Where,

L1 = concentration allowed to next batch, in mcg/g (or ppm)

LD50 = oral LD50 for detergent product (mg/kg)

BW = adult body weight (50 kg)

CF = conversion factor

LRDD = the maximum daily dose of the next manufactured drug product, in units

UW = mass of one unit (in grams)

❖ Note1: If multiple LD50 values are available based on different animal species, the lowest LD50 value available for human should be used.

❖ Note 2: CF is a combination of one factor to convert the LD50 to a NOAEL and a second safety factor. CF is 200,000 for oral applications and 2,000,000 for parenteral applications.

❖ Note 3: In this calculation, 1000 given in the numerator is to convert from mg to mcg.

L1 for the 100 ppm criterion

❖ L1 for the 100 ppm criterion is 100 mcg/g of detergent solids in the next product (the contribution of water in the detergent product is no relevant). The calculation for 100 mcg/g of detergent solids for L1 is as given below:

$$L1 = \frac{(100\ mcg/g)}{(\%\ solids)}$$

Where,

% solids = the percentage of non-water components of the detergent expressed as a decimal (for example, a detergent with a non-aqueous portion of 25% would utilize a value of 0.25 in this equation).

- Based on the smallest (most stringent) of the two L1 values calculated above, that criterion is used for the subsequent calculation for L2.

Calculation of L2 (total carryover per batch) is as below.

- Based on the smallest (most stringent) of the two L1 values calculated, that criterion (LD50-based and 100ppm) is used for the subsequent calculation for L2.

- For the LD50-based criterion, the L2 limit is calculated as given below:

$$L2 = \frac{(LD50) \times BW \times (Batch\ size)}{(CF) \times (LRDD)}$$

Where,

L2 = total carryover amount allowed to next batch, in milligrams (mg)

LD50 = oral LD50 for detergent product (mg/kg)

BW = adult body weight (50 kg)

Batch size = minimum batch size of next manufactured product, in units

CF = conversion factor to safety factor (typically 1,000 for all routes of administration)

LRDD = the maximum daily dose of the next manufactured drug product, in units

- Note1: If multiple LD50 values are available based on different animal species, the lowest LD50 value available for human should be used.

- Note 2: CF is a combination of one factor to convert the LD50 to a NOAEL and a second safety factor. CF is 200,000 for oral applications and 2,000,000 for parenteral applications.

For the 100 ppm criterion, the L2 limit is calculated as given below.

$$L2 = \frac{(100\ mcg/g) \times (Batch\ size) \times (UW)}{(\%\ solids) \times 1000}$$

Where,

L2 = total carryover amount allowed to next batch, in milligrams (mg)

Batch size = minimum batch size of the subsequently manufactured product, in units

UW = mass of one unit of next manufactured product, in grams

% solids = the percentage of non-water components of the detergent expressed as a decimal

- Note: In this calculation, 1000 in the denominator is to convert from mcg to mg.

Calculation of limit per surface area (L3) is as below.

- The L2 value calculated is then used for the subsequent calculation of L3 (limit per surface area) as given below:

$$L3 = \frac{(L2) \times 1000}{\text{(Surface Area)}}$$

Where,

L3 = limit per surface area, in mcg/in2

L2 = the L2 values in previous section, in milligrams (mg)

Surface area = total combined surface area of the product contact parts, in inch2

- Note: In this calculation, 1000 in the numerator is to convert from mg to mcg.

Calculation of limit per swab (L4a) is as below.

- For swab sampling, the limit per swab (L4a) is calculated as given below:

$$L4a = L3 \times \text{(Swab Area)}$$

Where,

L4a = limit per swab sample, in micrograms/swab (mcg/swab)

L3 = limit calculated in previous section

Swab Area = area swabbed, in inch2

Calculation of limit in rinse sample (L4c) is as below.

- For rinse sampling, the limit in a rinse sample swab (L4c) is calculated as given below:

$$L4c = \frac{L3 \times \text{(Rinse Area)}}{\text{(Rinse Amount)}}$$

Where,

L4c = limit in rinse sample, in micrograms/gram (mcg/g)

L3 = limit calculated in previous section

Rinse Area = area rinsed, in inch2

Rinse Amount = Amount (in grams) of liquid use for final rinse of equipment

- If all swab samples meet the acceptance limits determined as L4a limits for actives and detergent, the acceptance criteria are met.

- For any non-conforming result, an investigation should be performed to determine if the result is a valid result. The results of investigation should conclude the validity of result and consequential impact of result on conclusion of validation protocol.

- If either swab or rinse samples do not meet L4a limit or L4c limit for a given equipment item and that equipment is visually clean, then a stratified carryover calculation should be applied to that equipment to determine if the total cumulative maximum carryover to the next batch meets the L2 limit for that equipment train.

Staged (stratified) approach

Cumulative maximum carryover = Σ (MaxCn)

- Where for each of n equipment items in a train, the maximum carryover value (MaxC) for that equipment item, either as determined by a swab sample, is calculated as follows.

$$MaxC = \frac{(MaxSwab)\ X\ ESA}{(SSA)}$$

Where,

MaxSwab = highest L4a value for that equipment corrected for recovery factor

ESA = total surface area for that equipment

SSA = Swabbed surface area (typically 4 inch2)

- If the Cumulative Maximum Carryover for the train is less than L2, then the acceptance limit for that residue has been achieved. If the L2 criteria are not met, an out of specification comment should be logged for thorough investigation and impact assessment.

Limits for microorganisms and endotoxin

- For sampling using swabs, a bioburden acceptance criterion for Total Viable Count (TVC) shall be no more than a total of 50 CFU per 4 inch2 of sampled area. The CFUs on a plate that are yeasts/molds shall be no more than five (5); such an assessment of yeasts/molds may be done by a qualified microbiologist based on the morphology and appearance of the colonies on the cultured TVC plated.

- For rinse water sampling, bioburden acceptance criterion for Total Viable Count (TVC) shall be no greater than 100 CFU/mL. The CFUs on a plate that are yeasts/molds shall be no more than ten (10); such an assessment of yeasts/molds may be done by a qualified microbiologist based on the morphology and appearance of the colonies on the cultured TVC plates.

- Limits for endotoxin should be no more than 0.25 EU/mL in rinse samples only.

- **Approach on handling of potent products in shared facility (where the permitted daily exposure is less than or equal to 10 microgram per day)**

- The following special consideration should be considered in manufacturing such products:

    - It requires a greater level of personal protective equipment for operators.

- It may require special additional cleaning of equipment before validated cleaning and/or special protective equipment, as well as disposition of such personal protective equipment after cleaning.

- For potent drug manufacturing in shared facility, there can be two approaches.

  - In the first approach, a placebo batch of another product is made between the cleaning process and the subsequent manufacture of a different product, which is later discarded. After this, the equipment is cleaned and tested for residue of the previous product residue.

  - An alternative to this approach is to perform a second cleaning before manufacture of the next product, exactly like the first cleaning. This should be demonstrated by measuring the residue after the first cleaning and then again after the second cleaning. The data after the second cleaning is the actual relevant data for the protocol meeting its acceptance criterion. The desired outcome, however, is that the residue limit should be met after the first cleaning, and then should be even further reduced by the second cleaning. The second approach is less time consuming as compared to actually making a placebo batch.

- **Routine monitoring for potent products** : Additional testing is recommended for routine manufacture which would provide a higher degree of assurance of preventing cross-contamination for these higher risk products. Such testing might involve HPLC analysis of a final rinse solution where rinse sampling is applicable, or selection of at least one worst-case swab sampling location. That swab location should be the “worst case of the worst cases”. For example, a review of the original validation sampling locations might reveal one location which consistently passed, but consistently had higher residue values than the other locations.

- In routine manufacture, it is recommended to sample after the first cleaning, and if that result is acceptable, then not to perform additional testing after the second cleaning.

Use of software-based applications to identify worst-case products and calculate the MACO

- For facilities handling large number of products, it is recommended to opt for software-based applications to manage the product/equipment data matrix considering the changes, viz. addition/deletion of equipment, addition/deletion of new products, etc. Any software used should be qualified and validated as per GxP requirements.

Visual inspection

- Visually Clean (VC) is one criterion used to assess surface cleanliness. This criterion is significant in that if there is visible residue on the surface, then the equipment is not considered clean. The visual inspection is an active observation of all visually accessible product contact surfaces of the pharmaceutical manufacturing equipment after every cleaning.

- The purpose of visual inspection for cleaning validation is to detect not just particles, but any visual residues on the equipment surfaces that might be due to the cleaning process, including residue of the cleaned product and residue of the cleaning agent. The definition of visual inspection should also include issues not related to cleaning, such as rouge (iron oxide) and surface anomalies. Rouge and surface anomalies are not cleaning failures, but may be indicative of the need for equipment preventive maintenance.

- Visual inspection has elements of both an analytical method and a sampling method. It is typically used to supplement analytical method measurements in protocol or as part of a routine monitoring assessment. Whether a surface is considered visually clean depends on such factors as the viewing distance, lighting, angle of viewing, visual acuity of the observer and the contrast between the residue and the surface.

- To pass the test for visual cleanliness, the equipment must be free of product residue and detergent residue not inherent to the equipment. Residues other than those related to the cleaned product and the detergent used for cleaning do not constitute a cleaning protocol failure, but may require an investigation as to the source and determination of corrections and/or corrective actions.

- Visual inspection in a protocol involves extensive equipment disassembly to assure that critical surfaces are appropriately clean. Visual inspection for routine monitoring shall involve the same level of disassembly.

- **Establishing quantitative visual limits** : There is no need or requirement for establishing a quantitative visual limit for residues, unless visual examination is the only tool to determine that the residue is below its calculated limit.

- **Training for visual inspection** : Training for visual inspection should include an understanding of the relevant parameters (e.g., distance of viewing, angle of viewing, lighting type, and angle of added lighting) in making a visual inspection, the tools used for a visual inspection (e.g., a torch or a GoPro camera), and the need to examine key critical surfaces as well all readily visible surfaces. Examples of visually clean and visually soiled surfaces (as well as surfaces illustrating rouge and various surface anomalies) should be available for demonstration. These examples should preferably be actual surfaces (coupons), although digital photographs are appropriate for a written SOP. Persons doing a visual inspection should have acceptable vision and should not be color blind. At the end of training, qualification may include testing and rating by trainees of selected coupons with various levels and types of residues.

- The visual inspection of equipment has limitations in that some equipment surfaces (e.g., piping) are usually not accessible for viewing. The use of optical equipment like mirrors or endoscopes, as well as the use of additional lighting, can help to facilitate visual inspection.

- Remote inspection techniques (e.g., with fiber optic probes and a viewing screen) are utilized when visual inspection by a trained inspector is difficult to perform. Things that might make visual inspection difficult include issues related to tank entry, the hazards of a potential residue, or inaccessibility of critical equipment surfaces. Additionally, one might use remote inspection techniques to supplement an "unaided" visual inspection procedure.

- Borescopes, fiberscopes, and videoscopes allow visual inspection of hard to reach areas. Borescopes are used to view the interior of piping and tank welds. A benefit of such scopes is that they can fit into confined spaces not accessible to operators. They are very maneuverable, have additional lighting attached, and may come with optional magnification and/or zooming capabilities.

- The major drawbacks of these scopes are the difficulty of use, controlling lighting/brightness, and that the operator still has to make the determination if the area viewed is visually clean.

- **Cleaning operator qualification for cleaning (this refers to any person doing cleaning activity)**

- For manual cleaning, operator qualification for cleaning process is required in order for the operator to perform properly, and to ensure the rigor of the cleaning process and visual inspection.

- For qualification of cleaning operator, the following shall be considered; however, it should be remembered that these are not the only criteria for consideration:

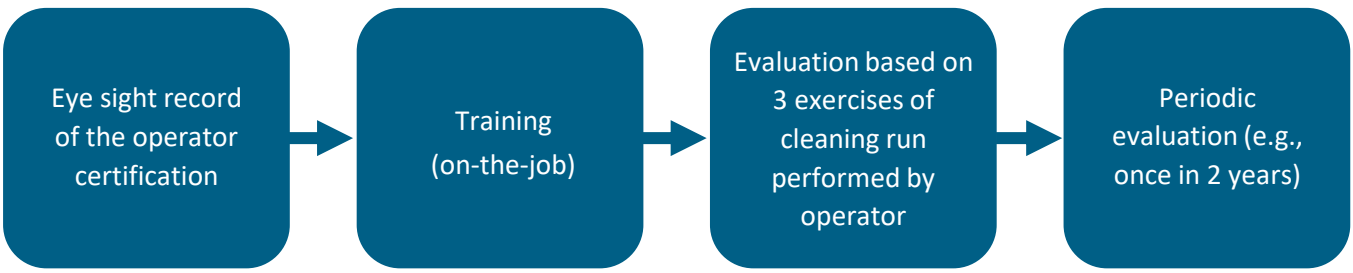
    - Eyesight record of the operator should be certified by a doctor, in order to ensure that the visually clean criteria of the machine surfaces are properly inspected.

    - During cleaning validation/verification programs and for routine inspections of cleaning effectiveness, visual inspection is one of the most important tools.

    - Visible cleanliness means the absence of any visible residue after cleaning. This is influenced by number of factors, of which the most obvious is the observer.

    - It does not depend only on the observer's visual capabilities but also the training imparted on what to observe and how to observe.

    - Visual inspectors shall be trained and qualified as per a properly defined procedure.



Flowchart for operator qualification

Points to be considered for training

- Operator cGMP training detail and on-the-job training, including practical demonstration of hard to clean locations.

- Training of operators to be carried out with respect to design of equipment in respect of complexity of product, and accessibility of areas which are difficult to clean.

- Discussion with operator in respect to type of cleaning, type of equipment, material of equipment like stainless steel, silicone gasket, Teflon, glass, PVC & HDPE, SOP related for particular equipment cleaning and level of cleanliness, etc.

- Information related to cleaning of equipment surface parts like roughness, texture, especially for ancillary equipment.

- Usage and retention period of cleaning tools and aids before process of cleaning.

- Verification of cleaned equipment by physical visual inspection, by using torch light or mirror if required.

- Perform operator qualification as per properly designed procedure.

- After completion of operator qualification, an appropriate certificate should be issued to the operator.

Evaluation

- Any three equipment should be selected for cleaning (including one with difficult to clean location) and qualification. Operator qualification shall be conducted on cleaning performed for equipment after product manufacturing.

- Successful cleaning followed by visual inspection verification by supervisor shall be used for concluding the operator qualification.

Re-qualification criteria

- Periodically (for example, once every two years ± 3 months), operator qualification for cleaning activity shall be performed for any one equipment. In case of failure in requalification, impact assessment followed by root cause analysis for appropriate CAPA shall be performed.

A typical template for Operator Qualification Procedure

Name of operator	
Department	
Facility	
Employee no.	

A) Pre-requisites

Sr. No.	Pre-requisites *	Observation	Observation recorded by Production
1.	Whether eyesight record of operator is available?		
2.	Whether eye-sight record of operator is certified by doctor?		
3.	Operator cGMP training details		
4.	Whether training of operators has been completed with respect to design of equipment in respect of complexity of product and accessibility of areas which are difficult to clean?		
5.	Has on-the-job training been completed, including practical demonstration of hard to clean locations?		
6.	Whether operator is trained for the required cleaning procedure?		
7.	Whether operator is trained for the operator qualification standard operating procedure?		
8.	Whether operator is trained on what to observe and how to observe?		
9.	Whether operator qualification procedure is going to be executed on commercial scale equipment?		

***Training must be completed before start of study.**

Operator (Signature/Date) : _____

Conclusion (please write whether operator can undergo further operator qualification procedure based on the information given above, attaching the training record/certificates wherever applicable).

Production Supervisor (Signature/Date) : _____

B) Type of equipment selection and cleaning details

Product name			
Batch no.			
Facility or line			
Type of equipment with equipment ID no.	Equipment I	Equipment II	Equipment III
Cleaning done on:			
Cleaning start time and date:			
Cleaning end time and date:			
Cleaning SOP no.			
Cleaning done by (cleaning operator) (Signature/date)			
Cleaning verified by (Production Supervisor) (Signature/date			

Type of equipment selection and cleaning details

Observation of equipment by operator after cleaning	Visually clean/Unclean	Visually clean/Unclean	Visually clean/Unclean
Observation of equipment by supervisor after cleaning	_____ Visually clean/Unclean	_____ Visually clean/Unclean	_____ Visually clean/Unclean
Qualified/Not qualified			

Comments :

Operator (Signature/Date) : _____

Comments :

Production Supervisor (Signature/Date): _____

Cleaning tools/aids

- Manual cleaning can be done with the use of cleaning aids. Brushes, scrubbers, and wipes of different sizes and functions are available, and these need to be defined and sourced. Examples of brushes include long and short-handle scrub brushes for cleaning flat surfaces, and large and small bottle brushes for cleaning valves and pipes. Non-abrasive, non-shedding scrubbing pads or wipes can also be used. All cleaning aids must be specifically selected. The cleaning aids shall be disposed of in case such aids are found to be damaged.

Ancillary equipment cleaning

- The cleaning processes and validation practices for ancillary equipment should not differ from the same practices utilized for direct impact manufacturing equipment as they present similar risk of cross-contamination.

Cleaning agents

- Cleaning involves removing an unwanted substance (the contaminant) from a surface (the equipment to be cleaned). Selecting cleaning agents is one of the first steps in developing a cleaning process.

- A variety of cleaning agents are available. These include water, organic solvents, commodity alkalis and acids, and formulated detergents.

Types

- **Water**
    - Although the typical use of water is in the pre-rinsing, post-rinsing, and preparation of use-dilutions, water is also used as a sole cleaning agent for readily water-soluble residues. As a general rule, the quality of water used in the final rinse should be at least as good as the water used in the manufacturing of the drug product. The water quality used in cleaning should also meet the chemical, microbiological and endotoxin levels as appropriate for the application.

- **Organic solvents**
    - Organic solvents, such as methanol, are used for cleaning in small-molecule API synthesis processes. Solvents are chosen based on the solubility of the manufacturing residues in the solvent. The cleaning process typically involves agitating the solvent in the reactor vessel, circulating it through pipes, and refluxing the heated solvent through overhead risers and condensers. The issue of flammability of organic solvents should be considered with care. Organic solvents, like isopropyl alcohol, are also used in finished pharmaceutical manufacturing for manual cleaning of parts and to facilitate drying of surfaces.

    - As per ICH Guideline Q3C (R6) on “Impurities: Guideline for Residual Solvents”, solvents in Class 3 (shown in Table below) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent that are known to be a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5000 ppm or 0.5% under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice.

Class 3 solvents which should be limited by GMP or other quality-based requirements.

Acetic acid	**Heptane**
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methyl ethyl ketone
Tert-Butyl methyl ether	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane

Commodity alkali

- A commodity alkali, such as sodium hydroxide, is often used for the alkaline wash step. The high pH and alkalinity of sodium hydroxide solutions may enhance solubility of organic process residues and, in some cases, facilitate hydrolysis. Sodium hydroxide is also widely available, relatively inexpensive and, being a single component containing no organic carbon, is relatively easy to analyze and validate for cleaning -agent removal. The higher pH of sodium hydroxide also facilitates the precipitation of salts or oxides of such ions as calcium, magnesium and iron if those ions are present during the cleaning process. However, commodity cleaners, such as sodium hydroxide, may have limited effectiveness for tenaciously adhered or baked-on residues. They also have limited wetting characteristics and residue suspending ability.

Commodity acids

- An acid washing step may be used alone for cleaning. The addition of an acid wash step after the caustic wash/rinse may overcome precipitation and buildup of inorganic compounds, improve rinsing, and help broaden the spectrum of residues cleaned (although at the expense of adding another cycle). In addition, maintaining a clean surface and limiting the deposition and build-up of iron oxides or other contaminants may help minimize the potential for stainless steel corrosion and rouge formation.

Formulated detergents

- Formulated detergents are multicomponent cleaning agents that take advantage of several different cleaning mechanisms, thus providing broader spectrum effectiveness. In addition to the mechanisms of alkalinity and hydrolysis offered by a commodity caustic, a formulated alkaline detergent might provide improved wetting and residue penetration, emulsification, chelation of calcium, iron oxide or other inorganic ions, and might facilitate dispersion of particulates in the wash step.

- Composition of detergent should be known together with change notification of critical changes (formulation guarantee from supplier). Technical agreement and vendor qualification are expected. Cleaning agent should be evaluated to meet local food standard during vendor qualification.

Test methods for actives and cleaning agents

- For residues of actives in finished drug products and for residues of detergents, validated analytical methods should be used to measure residues for which an acceptance limit is established.

- Methods may be either specific for the residue (such as HPLC) or may be non-specific for the residue (such as TOC). If a non-specific method is used, the non-specific method should be a direct measure of the target residue. For non-specific methods, the measured non-specific response shall be handled as if all of the response is due to the target residue.

- Methods for cleaning agents may be specific for a component in the detergent (such as the surfactant), or may be non-specific for a general property of the cleaning agent (such as conductivity).

- The preferred analytical methods are HPLC for actives and UV for detergents.

- Methods shall be validated using the principles of ICH Q2 (R1). When using a specific method, the specificity in the presence of possible interferences, including processing aids, detergents and sampling material, shall be evaluated. When using non-specific methods, the method should be validated, or suitability for use established, for a specific residue.

- Analytical methods should be validated for linearity at the residue limit in the analytical sample from the LOQ up the 150% limit value. The LOQ should be no more than 50% of that limit value.

- The Limit of Quantitation (LOQ) and Limits of Detection (LOD) should be established for each analytical method for chemical residues.

- Analytical methods may involve pass/fail tests, where the analytical method solely determines whether the sample is below the acceptance limit. Such tests allow more limited method validation consistent with ICH Q2 (R1).

- If an analytical method cannot measure down to the appropriate limit and the analytical method itself cannot be modified or changed to obtain an appropriate LOD/LOQ, the following may be considered to increase the limit in the analytical sample:

    - Extracting the swab with a smaller amount of solvent.

    - Sampling a larger surface area (16 in2 instead of 4 in2).

    - Using a smaller rinse volume for rinse sampling.

    - Increasing the batch size of the next product.

    - Restricting the order of manufacture of products.

- If a new analytical method cannot be developed or if the calculated limits cannot be adjusted upward, then the product shall be made on dedicated equipment.

4.1.2.5 Analytical method validation:

- Analytical method validation and recovery study shall be performed once the composition, manufacturing and cleaning procedure of drug substances and drug product is finalized.

- The method of analysis from finish product test procedure should be selected. First choice is the existing assay/RS/dissolution method by modifying injection volume if required to achieve at least 50% lower LOQ than swab maximum allowed residue (MAR) value. If the method is not working, it is necessary to develop a new method using more sensitive instrument like LCMS/MS.

- After selection of analytical cleaning methodology, analytical method validation and recovery study for cleaning validation sample should be carried out.

- Key parameters to be measured in analytical method validation for the cleaning validation sample are:

    - Specificity.
    - LOD and LOQ determination.
    - LOQ precision.
    - Linearity and range.
    - Recovery on different plates at LOQ to 150% of MAR value.
    - Solution stability.

Specificity

- **Definition** : Specificity of an analytical method is its ability to measure accurately and specifically the analyte of interest without interferences from blank, blank swab and placebo.

- **Blank swab preparation** : The head of the swab should be allowed to fall into a suitable test tube, and the desired volume of medium (diluent) should be added.

- **Placebo preparation** : Placebo powder should be weighed accurately and then transferred and diluted up to mark with medium (diluent), in order to achieve the concentration of 10 ppm corresponding to label claim of active content.

- **Acceptance criteria** : There should be no interference from swab/blank, placebo and detergent.

- Determination of LOD and LOQ

- **Definition** :

- **LOD: Limit of detection.**

- The limit of detection is the lowest concentration of the analyte in a sample that can be detected, but not necessarily quantified, under the stated experimental conditions.

LOQ: Limit of quantitation.

- The limit of quantitation is the lowest concentration of the analyte in a sample that can be determined with acceptable precision and accuracy under the stated experimental conditions.

- In order to determine LOD and LOQ, solutions of standards at different concentration levels should be injected, and LOD and LOQ will be measured by examining the slope and regression line or by using the signal-to-noise ratio method.

Acceptance criteria for LOD and LOQ

- Signal-to-noise ratio for limit of detection should be about 3:1.

- Signal-to-noise ratio for limit of quantitation should be about 10:1.

- The obtained LOQ value should be at least 50% of MAR value.

Precision of LOQ

LOQ standard preparation

- Prepare a standard solution as per required concentration in determination of LOD and LOQ.

Acceptance criteria

- The % RSD of six replicate injections at LOQ level should not be more than 15.0%.

Linearity and range

- **Linearity** : The linearity of an analytical method is its ability to elicit test results that are directly, or by well-defined mathematical transformation, proportional to the concentration of analyte in sample within a given reference range.

- **Range** : The range of an analytical method is the interval between the upper and lower levels of analyte (including these levels) that have been demonstrated to be determined with precision, accuracy and linearity using the method as written. The range is normally expressed in the same units as test results (e.g., percentage, parts per million, etc.) obtained by the analytical method.

- Linearity test should be performed at minimum 5 levels over the range of LOQ to 150%.

Acceptance criteria

- The correlation coefficient (r) should not be less than 0.990 over the working range.

Recovery study

Definition :

- The accuracy of an analytical method is the closeness of test results obtained by that method to the true value. The true value is that result which would be observed in the absence of error. Accuracy may often be expressed as percentage recovery by determination of known added amounts of analyte.

- Accuracy tests should be performed on different MOC of equipment like stainless steel, glass, PFA, Halar, Teflon, plastic, Tefzel, acrylic, neoprene, EPDM, Hypalon, silicon and PP plate. Accuracy tests should be performed in triplicate at the minimum of each of four levels (LOQ, 50% of the limit, 100% of the limit, and 150% of the limit).

Coating and drying

- The desired volume should be spread with the help of a pipette on a predefined template of the respective plate and the solvent should be allowed to evaporate.

- After swabbing, the active content should be extracted from the swab in a glass vessel with the medium (diluent) in order to achieve concentration at each of four levels (LOQ, 50% of the limit, 100% of the limit, and 150% of the limit).

- Swabbing shall be done in accordance with the procedure described in an earlier section of this Best Practices Document.

- This procedure should be performed for all recovery test preparations.

Acceptance Criteria

- Individual recovery and mean recovery scores shall be NLT 70% for all surfaces in the concentration range other than LOQ. For LOQ it shall be NLT 50%.

Stability Study

- The solution stability of standard solution should be determined at between 2 to 8° C and at room temperature for up to 72hours.

Swab sample solution stability study (to be performed for any one plate)

- Swab recovery sample solution of 100% obtained during the recovery study should be kept at between 2 to 8° C and at room temperature for up to 72hours.

Acceptance Criteria

- The difference in the initial value and value obtained after specific interval for swab recovery solutions should not be more than 5.0% (Absolute).

Swab sample stability study (to be performed for any one plate)

1. The desire volume (in ml) of the recovery study solution at 100% level should be spread on template of the specified area, and the solvent should be allowed to evaporate by using a hair dryer.

2. The area should be swabbed vertically and horizontally in a unidirectional method, so as to cover the entire surface, with Texwipe swab moistened with 1 ml of purified water.

3. The above swab should be kept for 72 hours (at below 27° C and between 2 to 8° C), and the swab recovery solution prepared as per procedure given in recovery study.

4. The same procedure should be followed for 72 hours in order to study swab sample stability.

Acceptance criteria

- The recovery results in the initial value and value obtained after specific interval for swab recovery solutions should not be less than 70%.

Test methods for bioburden

- Microbiological methods for bioburden and endotoxin that are from pharmacopeias do not require further validation. Any in-house procedure should be approved and validated.

Detergent interference with HPLC method for actives:

- The detergent may interfere with HPLC analysis either by changing the separation characteristics of the active (for example, change in retention time) or by contributing to detector response where UV is used as the detection method in HPLC. This can be evaluated in the lab by preparing known standards of the active at its limit, and adding an amount of detergent that may be present at its limit, and then comparing the HPLC response of a spiked sample with that of an unspiked control. This should be done for all current methods, as well as for new methods developed in the future. However, it should be noted that a positive contribution of detergent is acceptable; it indicates that the measured amount of active by the HPLC method may actually represent a worst-case as compared to the actual amount present.

Multiple operators for recovery determination

- **Option 1** : One person in the analytical lab should perform recovery studies, with three replicates at each of four levels (LOQ, 50% of the limit, 100% of the limit, and 150% of the limit).

- **Option 2 :** Three persons in the analytical lab should perform recovery studies, with three replicates at any one level (preferably LOQ 100% of the limit).

4.1.3 Phase 3: Continued cleaning verifications (ongoing cleaning verifications)

- During this phase the cleaning process is monitored to ensure that it is operating in the state of control. The main aspects are:

  - **Ongoing cleaning monitoring** : Through process monitoring, unplanned events representing a departure from the validated process can be detected. These can be trended to see the shifts in cleaning method performance. This monitoring program can be risk based and can be a subset of tests utilized during the cleaning validation. This shall include the sampling plan and the list of all the analytical methods to be used.

  - It is recommended that this routine be followed wherever multiple products are handled in a shared facility, preferably when a product changeover is happening from highly potent to low potent products.

  - For products where the PDE is equal to or less 10 micrograms per day, it is recommended that a cleaning verification be performed after every changeover.

  - **Periodic reviews (monitoring of process capabilities)** : This should be performed as part of validation life cycle. The intention of this to demonstrate that the cleaning process remains in the validated state of control, and, if needed as an outcome of review recommendation, process improvement or revalidation can be done if process is found to be out of control.

  - It is recommended that cleaning verification results and calculated process capability data be used to support this. For example, the results from cleaning verification sample analysis could be statistically trended. The capability of the cleaning process is then calculated by using an appropriate statistical process. Data should be presented, for example, in graphical form, and the capability of the process in relation to control limits and the margin of safety should be presented and discussed as part of continuous improvement over the lifecycle.

  - Example of periodic review is given in a subsequent section.

  - **Reviewing of deviations and changes**
  - Validated cleaning process is subject to change control. In addition, any unexpected events/failures should be recorded as deviations or OOS. These should be investigated to assess the probable causes and possible corrections in order to bring the cleaning process back to the state of control. Preventive maintenance and calibration programs keep equipment and instruments operating correctly and in calibrated state. These programs may have an impact on the cleaning performances of equipment/instrument; hence it is recommended that an assessment be done of the preventive maintenance process and protocol with respect to its impact to cleaning process.

- Knowledge gained during this phase may require the organization to go back to Stage 1 for further development or for revalidation at Stage 2. These are part of the feedback and feedforward mechanism of the lifecycle approach, applicable to all stages of cleaning validation.

- The cleaning procedure should remain in a validated state. Cleaning verification and process capability may be used to provide data to support this. For example, the results from cleaning verification sample analysis could be statistically trended. The capability of the cleaning process is then calculated through an appropriate statistical process.

- The presentation of individual results and data used in the calculation, such as with a Central Processing Unit (CPU) and acceptable daily exposure (ADE) base limit, should meet ALCOA principles. Data should be presented, for example, in graphical form, and the capability of the process in relation to control limits and the margin of safety should be discussed as part of continuous improvement.

Quality metrics and performance indicators

- Aspects of HBELs setting, cleanability studies, cleaning validation and cleaning verification, as well as process capability, should be considered in quality metrics, with performance indicators identified which be monitored.

Example of a template for conducting periodic reviews of cleaning process validation/verification

1.0 Objective

- It is intended to conduct periodic review of cleaning validation results in order to demonstrate that the cleaning process remains in the validated state of control, and, if needed as an outcome of review recommendation, process improvement or revalidation can be done if process is found to be out of control.

2.0 Review of change history

- Details of change controls that have been initiated with respect to revision of cleaning procedures will be examined.

3.0 Review of failures

- Any failures reported during the review period, such as deviation, OOS/OOT, lab incidents during cleaning verification/validation studies, shall be reviewed including the investigation outcomes attributed to cleaning failures.

4.0 CAPA and its effectiveness check

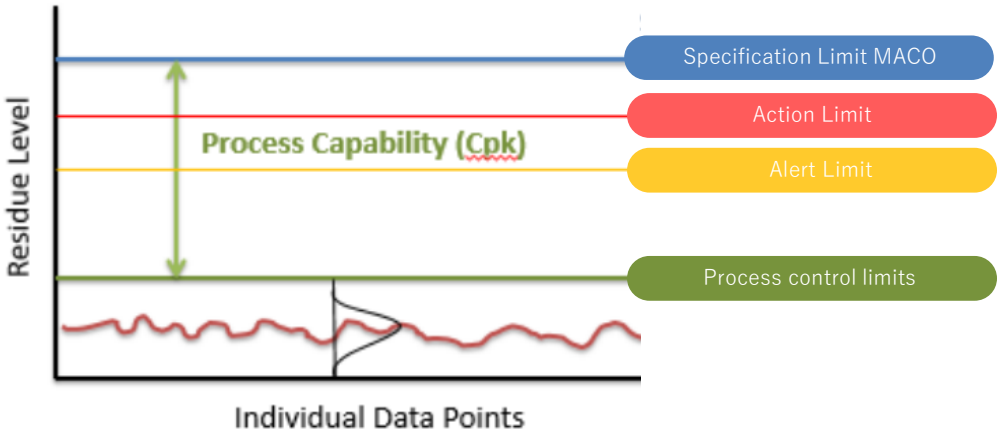
- Details of CAPA (if any) initiated with respect to revision of cleaning procedures and outcome including effectiveness checks will be examined.

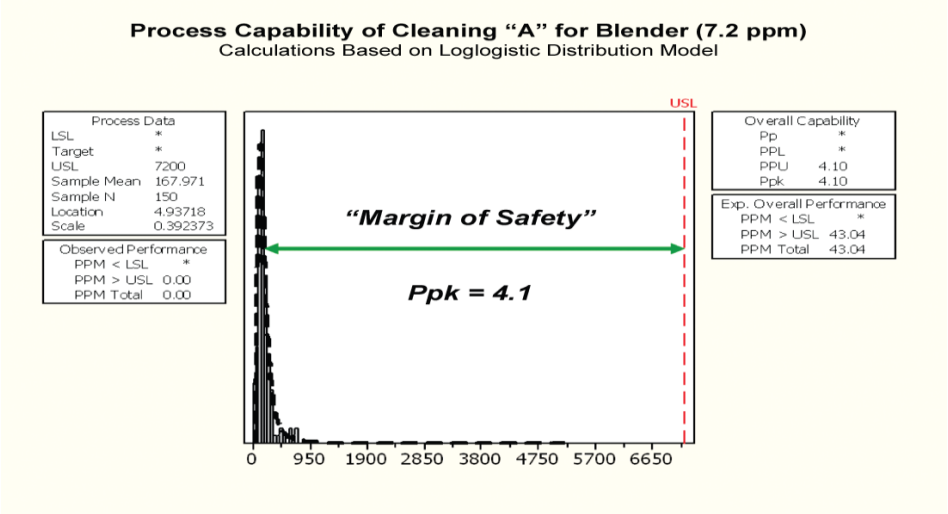
5.0 Statistical evaluation of cleaning verification/validation

- The statistical evaluation should be done for residue results observed during cleaning verification/validation of each equipment/equipment groups cleaned by a specific cleaning procedure.

- The trending study may include plotting the graph to monitor the residues observed and evaluating the data against possible control limits derived on the basis of sufficient number of data points (as an example, a minimum data set of 20 or more residue results should be taken).

- The analysis should include assessment based on comparison of routine results against the cleaning validation data. An alert and action limits should be established based on historical data. Process control limits, viz. mean results plus four standard deviations can be considered. If any drift is noted on the number of data points (either with an increasing or a decreasing skew), a next level investigation/assessment should be done to find out possible root causes and areas of improvement.





6.0 Recommendation from the periodic review

- Any recommendation based on the outcome of periodic review will be taken into account. Recommendations may include actions for improvement and/or monitoring for a number of cleaning process, or the need of investigation of the cleaning procedure specific to any equipment or product.

7.0 Attachment (if any)

Other considerations

Campaign production

- A campaign is a series of batches of the same product manufactured one after the other. When considering campaigns, it is usually the case that when one campaign is ended and another one is started, cleaning validation is required to prevent cross-contamination of different products.

- Consideration should be given to the need to clean, and the extent of cleaning, between batches in a campaign.

- A worst-case condition takes into consideration the residue attributes, campaign durations, campaign frequency, time between regular cleaning events, dirty equipment hold and interruption times between batches. Product quality and residues carried into subsequent batches should be considered as part of the cleaning validation approach.

- Depending on the product, there may be no cleaning between batches or some level of cleaning between batches may be done. If the cleaning between batches is simply a vacuuming (for solid products) or a solvent or water rinse (for liquid products), such cleaning is sometimes called “minor cleaning” or “in process cleaning”. Such minor or in process cleaning steps do not require separate validation based on the risk assessment approach. However, consideration should be given to the effect of such minor or in process cleaning steps on the efficiency of the “full cleaning” process done at the end of a campaign for changeover to a new product or campaign.

- If only the cleaning process at the end of the campaign is to be validated, consideration should also be given to the number of batches and/or the total elapsed time for a campaign. The campaign length for solid oral products can be batches manufactured over a period of six (6) days, or the number of batches manufactured wherein there is minimum possibility of increase in microbial load due to the nature of composition used and the environmental condition of manufacturing areas.

Hold times

Dirty hold time

- The dirty hold time (DHT) is a cleaning process challenge that is defined as the time from the end of manufacture until the beginning of the wet cleaning process.

- A DHT shall be specified in the validation protocol for a product or a group of products. The DHT for a representative product in a product group shall be applied to all products in that group as the maximum DHT for routine manufacture.

- For all formulation types, a maximum DHT shall be established based on a protocol using the worst-case product in a group.

- The DHT for a previously validated process may be extended by performing a DHT verification protocol on the worst-case product over a longer time period. If the residue results for the active are no more than 50% of the limit, then the longer DHT is validated.

Clean hold time

- The clean hold time (CHT) is defined as the time from the end of the validated Type B cleaning process until the beginning of the use of that equipment for manufacture of products. The CHT may be performed as part of the cleaning process validation protocol or may be performed as a stand-alone protocol apart from the cleaning validation protocol.

- In a protocol, the CHT assessment involves leaving the equipment unused under normal conditions, and then measuring any changes in equipment related to visual appearance and to bioburden proliferation. The acceptance criteria are that the equipment shall be visually clean at the end of the CHT and that the bioburden is no more 50 CFU/4 inch2.

- If the manufactured product that has significant higher bioburden (for example, because it has an active/excipient that is a natural product extract), that product should be considered for CEHT protocol. For parenteral products, BET should also be considered as criteria for CHT.

- Because CHT is independent of the product manufactured, provided the equipment is cleaned, and meets the applicable acceptance criterion, and is stored under the same external condition and location, one CHT protocol on a representative equipment may be applied to all equipment in a defined group.

- The CHT for a previously validated process may be extended by performing a CHT verification protocol on any product in the group over a longer time period. If the equipment is visually clean, and if the bioburden results are no more than 50 CFU/4 inch2, then the longer CHT is validated.

- Dedicated equipment should also be considered for doing DHT and CHT studies.

Annexure

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

Type-B Cleaning Checklist FBD/FBP 500-800 Liter

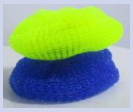
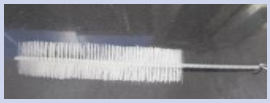
Equipment Name:		Capacity	
Equipment ID:		Room ID:	
Previous Product		Batch No:	

Instruction for checklist execution:

- Write “YES” in status column - for completion of activity
- Write “NA” in status column - if step is Not Applicable
- Write “NO” in status column - for activity not completed
- If activity is not completed as per instruction then production supervisor shall re-issue the checklist and operator shall again perform cleaning activity.
- If more than one person has performed the cleaning, step number performed by individual doer shall be mentioned in remarks (at the end of checklist) with signature and date.
- Put a tick mark if Yes and if No
- Perform washing process for minimum time specified in individual step. Continue washing for additional time if any visible product residue is observed.

Instructions for Usage of Cleaning Agent

- Use 5% KOH solution for scrubbing where Eudragit is used during manufacturing of previous product.
- Use Acetone for scrubbing where Omeprazole Enteric coating (Polymer material-Hypromellose Phthalate) is used during manufacturing of previous product.
- In all other cases use 1.0 % v/v Hemtop solution.
- Cover entire accessible equipment surface during scrubbing & continue scrubbing till surface is free of adhered material. Use plenty of process water during scrubbing if required

Cleaning Aids				
Nylon Scrubber 	Nylon Brush 	Scrapper 	Vacuum Cleaner 	
High Pressure Jet 	Telescopic Pole 	Lint Free Cloth	1.0 % v/v Hemtop solution	
			Acetone	
			5% KOH solution	
Start Date/Time:	__/__/__	__:__	Done By (Sign/Date):	

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

Sr. No.	Cleaning Steps	Status (Yes /No /NA)
1.0	Ensure that "TO BE CLEANED" label is affixed on the machine	
2.0	Record the cleaning start time details in sequential logbook	
3.0	**Initial Dry Cleaning/Dismantling:**	
3.1	Remove the adhering material of the Finger bag by repetitive shaking in manual mode **OR**	
	Go to 'GENERAL' function and select 'Filter' then pressing 'Blow out filter manually' icon for manually shaking	
3.2	Remove the Spray gun assembly from gun port, Silicon tubes, Atomization air pipe from Spray gun assembly (Applicable for Top Spray / Bottom Spray Arrangement	
3.3	Remove hose pipe from the charging and discharging assembly	
3.4	Transfer the hose pipe and silicon tube in washing area in polybag with "To be Cleaned Label "and Clean the hose pipes and silicon pipe as per SOP No. XXXX	
3.5	Detach the product sensor	
3.6	Deflate the product container through HMI/MMI/IPC and slide out it from machine	
3.7	Deflate the finger Bag by pressing deflate button on HMI/MMI/IPC	
3.8	Bring down the finger bag assembly manually or from HMI/MMI/IPC	
3.9	Detach the finger bag by opening the clamps or SS belt and gaskets from finger bag holding assembly. Check the wear and tear of the bag and gaskets visually	
3.10	Collect the finge r bag in polythene bag and close the bag with cable tie and transfer it to the wash area with "To be cleaned label" in closed cond ition. Clean the Finger bag as per SOP No. XXXX	

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

Sr. No.	Cleaning Steps	Status (Yes /No /NA)
3.11	Clean the HMI/MMI/IPC, Sensors, FLP Lamp, pneumatic tubes, Electrical wires and switches with dry lint free cloth followed by wet lint free cloth and cover with polybag	
3.12	Clean the Peristaltic pump, trolley and balance display with dry lint free cloth followed by wet lint free cloth and cover with polybag ***(Applicable for Top Spray / Bottom Spray Arrangement only)***	
3.13	Open the **exhaust air flap** by "On/Off" selector switch	
3.14	Remove the sealing gasket of the expansion chamber and lower plenum	
3.15	Remove adhered previous product remnants from the internal & external surfaces of lower plenum, product bowls, and expansion chamber with the help of vacuum cleaner/lint free cloth. Scrap the adhered material with Teflon scrapper, if required.	
3.16	Remove all loosely stuck powder from the atomization pipes, transmitter (wherever applicable) with dry lint free cloth followed by wet lint free cloth and cover with polybag.	
3.17	Collect the material in double polythene bag and Affix the "**REJECT TO BE DESTROYED LABEL**" on collected scrap material and transfer it to reject bin	
3.18	Switch "off" the FBD/FBP from panel or by using emergency button (If required switch on the FBD/FBP during cleaning)	
Done By (Sign/Date):		
4.0	**Pre-Wash/Initial Wash :** Coverentire surface during pre-washing	
4.1	Connect the High Pressure Jet Cleaning Machine with process water supply line	
4.2	Open the drain valve of FBD/FBP	
4.3	Connect the process water supply with supply pipe of FBD/FBP for flushing inner surfaces of expansion chamber ***(Applicable for WIP only)***	

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

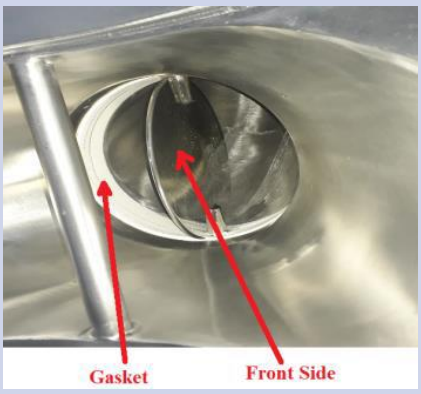
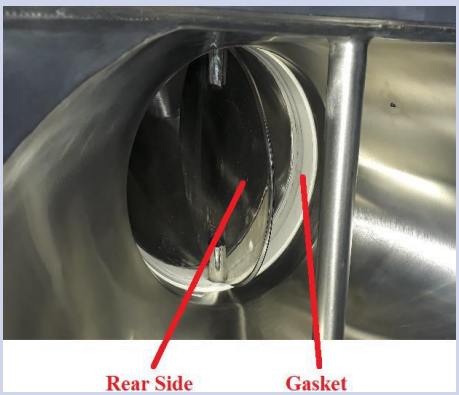
Sr. No.	Cleaning Steps	Status (Yes /No /NA)
4.4	Switch “ON” the high pressure jet cleaning machine and set the pressure NLT 50 bar by adjusting the knob	
4.5	Flush the **exhaust duct flap**(as applicable) with process water	
4.6	Flush the outer surface of **inlet/exhaust air duct**(as applicable) with process water	
4.7	Flush the internal and external surfaces of expansion chamber from top to bottom, gun port, charging/discharging port and finger bag holding assembly with process water.	
4.8	Flush the internal and external surfaces of lower plenum, drain pipe/valve with process water	
4.9	Flush the Product Bowls and its accessories, from inside and outside and its wheel with process water.	
4.10	Flush the Dutch mesh sieves, base plate and support cross with process water	
Done By (Sign/Date):		
5.0	**Done By (Sign/Date):**	
5.1	Bowl No. 01 ID | Bowl No. 02 ID Open the clamps and dismantle following parts from the product container bowls: Base Plate, Dutch mesh assembly, Support cross, Sampling Port, View Glass(es) and Discharging Port	
5.2	Dismantle the View Glass(es) and its gasket, gun port and discharging port of expansion chamber.	
5.3	Dismantle the mini column (for bottom spray only), Spray Gun cylinder, Spray Gun, Nozzles, spray gun cylinders, Manifold, O-rings and its accessories like nut-bolts, clamps ***(Applicablefor Top Spray/Bottom Spray Arrangement only)***	
5.4	Dismantle the Product Sampler Articulated clamps, Holding bottles, Push rod from the product container bowl ***(Applicable for Bottom Spray Arrangement only)***	

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

Sr. No.	Cleaning Steps	Status (Yes /No /NA)
5.5	Dismantle the Charging assembly, discharge assembly of cyclone separator/ Vacuum transfer system (VTS), bag and its clamps and transfer the bag to wash area with in double polybag with "**TO BE CLEANED LABEL**"	
5.6	Dip the dismantled parts including dismantled nut bolt/clamps and gasket (except Dutch mesh, base plate, and support cross) in container containing Process water/5% KOH solution/Acetone (as applicable).	
Done By (Sign/Date):		
6.0	**Scrubbing of Equipment Parts:**	
6.1	Scrub the internal surfaces of expansion chamber from top to bottom, gun port, discharging port and finger bag holding assembly with the help of Telescopic pole with scrubber	
6.2	Scrub the inner and outer surfaces of lower plenum and drain pipe/valve with nylon scrubber/brush	
6.3	Scrub the Product Bowls, Column (for bottom spray only), sampling port and holding clamps, bowl trolleywith nylon scrubber	
6.4	Scrub the Charging assembly, discharge assembly of cyclone separator/Vacuum transfer system (VTS)and its clamps with nylon brush/scrubber	
6.5	Scrub the gaskets, Dutch mesh assembly, sampling bottle, base plate, support cross, view glass(es), gun port, nut-bolts, clamps and scoop (if used) with nylon scrubber	
6.6	Scrub the Spray Gun cylinder, Spray Gun, Nozzles, spray gun cylinders, Manifold, O-rings and its accessories. ***(Applicable for Top Spray Arrangement only)***	
6.7	Scrub the mini column, spray gun cylinder, Spray gun, nozzles and manifold, Product Sampler Articulated clamps, Holding bottles, Push rod with nylon brush. ***(Applicable for Bottom Spray Arrangement only)***	

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

Sr. No.	Cleaning Steps				Status (Yes /No /NA)
Done By (Sign/Date):					
7.0	**Washing of Equipment Parts::**				
7.1	Switch “ON” the High Pressure Jet Cleaning Machine and set the pressure about NLT 50 bar by adjusting the knob. Ensure High Pressure Jet Cleaning Machine connected with process water supply line.				
7.2	Wash the **exhaust air duct flap**(as applicable)for NLT 02 minutes				
	Pressure		**Time**		
7.3	Wash the outer surface of **inlet & exhaust air duct**for NLT 02 minutes				
	Pressure		**Time**		
7.4	Wash theinternal and external surfaces of expansion chamber from top to bottom, gun port, charging port and finger bag holding assembly for NLT 05minutes				
	Pressure		**Time**		
7.5	Wash the internal and external surfaces of lower plenum, drain pipe/valve for NLT 05minutes				
	Pressure		**Time**		
7.6	Wash the Product Bowls from inside and outside, Columns (for bottom spray only), holding clamps, bowl trolley and wheels for NLT 10minutes				
	Pressure		**Time**		
7.7	Wash the Charging assembly, discharge assembly of cyclone separator/Vacuum transfer system (VTS)and itsclamps for NLT 03minutes				
	Pressure		**Time**		

Sr. No.	Cleaning Steps				Status (Yes /No /NA)
7.8	Wash the Gaskets, Dutch mesh assembly, sampling bottle, base plate, support cross, view glass, gun port, nut-bolts, clamps and scoop (if used) for NLT 08minutes				
	Pressure		**Time**		
7.9	Wash the Spray Gun cylinder, Spray Gun, Nozzles, spray gun cylinders, Manifold, O-rings and its accessories by dipping in process water ***(Applicable for Top Spray Arrangement only)***				
7.10	Wash the mini column, spray gun cylinder, Spray gun, nozzles and manifold, Product Sampler Articulated clamps, Holding bottles, Push rod by dipping in process water ***(Applicable for Bottom Spray Arrangement only)***				
Done By (Sign/Date):					
8.0	**Cleaning of Inlet Air Duct and Flap:**				
8.1	Open the Inlet air duct flap manually by changing the pneumatic tubes or through selector switch HMI/MMI/IPC.				
8.2	Flush the**inlet air duct up-to bent** and both sides of **damper /flap**, gasket with process water using high pressure jet.				
8.3	Scrub the**inlet air duct flapwith 1.0 v/v Hemtop**from both sides and gasket rim with nylon scrubber.  				

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

Sr. No.	Cleaning Steps				Status (Yes /No /NA)
8.4	Wash the **inletair duct up-to bent and flap** with process water for NLT 03 minutes				
	Pressure		**Time**		
8.5	Wash the inlet lower plenum and drain pipe with process water using high pressure jet until visible residue is removed				
8.6	Rinse the **inlet air duct and flap** with purified water for NLT 01 minute				
	Pressure		**Time**		
8.7	Use torch light **inlet air duct up-to bent** to visually check the residue.				
8.8	Close the Inlet air duct flap through selectorswitch provided on HMI/MMI/IPC panel.				
Checked & Recorded By (Sign/Date):			**Done By (Sign/Date):**		
9.0	**Initial Inspection:**				
9.1	Inspect the View Glass(es) including Gasket in dismantled condition				
9.2	Inspect the equipment, inlet air duct and dismantled parts for any visible residue after washing. If complies proceed for next step else repeat the particular washing steps and record the cleaning details in remark below with step number.				
Cleaning Status (Complies/Not Complies):			**Inspected By (Sign/Date):**		
Remarks					
Cleaned By:					

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

Sr. No.	Cleaning Steps				Status (Yes /No /NA)
Done By (Sign/Date):					
10.0	**Purified Water Rinsing of Equipment Parts:**				
10.1	Connect the high pressure jet cleaning machine with purified water supply and set the pressure about NLT 50 bar ⍰ by adjusting the knob.				
10.2	Rinse the **exhaust air duct flap**(as applicable)for NLT 01 minute				
	Pressure		**Time**		
10.3	Rinse the outer surface of inlet/exhaust air duct for NLT 01 minute				
	Pressure		**Time**		
10.4	Rinse the internal and external surfaces of expansion chamber from top to bottom, gun port, charging/discharging port and finger bag holding assembly for NLT 02minute				
	Pressure		**Time**		
10.5	Rinse of internal and external surfaces of lower plenum, drain pipe/valve for NLT 02minute				
	Pressure		**Time**		
10.6	Rinse the Product Bowls from inside and outside, Columns (for bottom spray only), holding clamps, bowl trolleyand wheels for NLT 04minutes				
	Pressure		**Time**		
10.7	Rinse the Charging assembly, discharge assembly of cyclone separator/Vacuum transfer system (VTS)and its clamps for NLT 02minute				
	Pressure		**Time**		
10.8	Rinse the gaskets, Dutch mesh assembly, sampling bottle, base plate, support cross, view glass, gun port, nut-bolts, clamps and scoop (if used) for 04minutes				
	Pressure		**Time**		

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

Sr. No.	Cleaning Steps	Status (Yes /No /NA)
10.9	Rinse the Spray Gun cylinder, Spray Gun, Nozzles, spray gun cylinders, Manifold, O-rings and its accessories by dipping in purified water.***(Applicable for Top Spray Arrangement only)***	
10.10	Rinse the mini column, spray gun cylinder, Spray gun, nozzles and manifold, Product Sampler Articulated clamps, Holding bottles, Push rod by dipping in purified water. ***(Applicable for Bottom Spray Arrangement only)***	
Checked & Recorded By (Sign/Date):		**Done By (Sign/Date):**
11.0	**Drying:**	
11.1	Dry the Lower plenum, inlet air duct flap and Product Bowls with compressed air. Use dry lint free cloth, if required.	
11.2	Dry the exhaust air duct flap with drylint free cloth	
11.3	Dry the dismantled parts of FBD/FBP with compressed air. Use dry lint free cloth, if required.	
11.4	Remove the polybag from the HMI/MMI/IPC, peristaltic pump (for top/bottom spray only), Sensors, Electrical switches, FLP Lamp, and balance display.	
11.5	Wipe the panel board HMI/MMI/IPC, peristaltic pump, trolley(for top/bottom spray only) Sensors, Electrical switches, wires, FLP Lamp and balance display using dry lint free cloth.	
11.6	Ensure surrounding area is cleaned as per SOP No. **XXXX**	
11.7	Assemble the dismantled parts of Product Bowl No. 01 and Product Bowl No. 02 (as applicable) and tightened the clamps.	
11.8	Slide in the product container bowl in main body and Switch ON the FBD/FBP.	

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

Sr. No.	Cleaning Steps				Status (Yes /No /NA)
11.9	Start the drying process by setting inlet temperature at 60-80°C to dry the chamber & Product Bowls for 15-20 minutes in empty condition.				
	Bowl No. 01 ID		**Time**		
	Bowl No. 01 ID		**Time**		
11.10	Ensure completeness of cleaning of, tool box, Waste Bin (It should be empty and clean) and Reject Bin. Affix the duly signed 'CLEANED' label on the equipment.				
11.11	Record the cleaning end time details in the "Sequential logbook.				
End Date/Time:			**Done By (Sign/Date):**		
Remarks, if any:					
Review By (Sign/Date):					

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

Break Start Time	Step No.: till completed	Reason for break	Done By	Verified By

Equipment Cleaning Verification/Visual Inspection (SOP No.: XXXX

- Use Torch Light for Inspection

- Identify the component for inspection in Photograph album by comparing Photo sr. no. mentioned below. Physically check the component against Album and certify for visual cleanliness.

- Write " Yes" for complies and "No" for not complies and NA for not applicable in observation column.

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

12.0	Photo Sr. No.	Component / Area of Inspection	Production	QA
			Observation (Yes /No/NA)	Observation (Yes /No/NA
12.1	1	Lower Plenum/ Plenum Rim		
12.2	2	Inlet Duct Flap with Gasket		
12.3	3	Drain Hole		
12.4	4	Drain Pipe		
12.5	5	Filter Bag Holding Assembly		
12.6	6	Gasket –Filter Bag Ring Assembly		
12.7	7	SS Belt for Filter Bag tightening		
12.8	8	Expansion Chamber		
12.9	9	Spray Gun Port		
12.10	10	Material Charging Port –Expansion Chamber		
12.11	11	Product Container Bowl (Container Bowl/Wruster)		
12.12	12	Sampling Port with Triclover		
12.13	13	Holding Clamps to Dutch Mesh & Holding Plate		
12.14	14	Dutch Weave Holding Plate		
12.15	15	Dutch Weave Mesh		

12.0	Photo Sr. No.	Component / Area of Inspection	Production	QA
			Observation (Yes /No/NA)	Observation (Yes /No/NA
12.16	16	Dutch Weave Holding Support Cross		
12.17	17	Nuts to fit Mesh & Holding Plate to Bowl Rim		
12.18	18	View Glass(es) & its Gaskets (assembled condition)		
12.19	19	Product Temperature Sensor Port		
12.20	20	Product Temperature Sensor		
12.21	21	Material Discharging Port –Product Bowl		
12.22	22	Flameproof Lamp		
12.23	23	Peristaltic Pump & Manifold		
12.24	24	Spray Gun & Nozzle Assembly		
12.25	25	Gasket (O-Ring) -Spray Gun & Nozzle Assembly		
12.26	26	Inflatable Sealing Gaskets		
12.27	27	Exhaust Duct Outer Surface		
12.28	28	Portion Segment connected between Lower Plenum till Damper / Pneumatic Operated Flap		
12.29	29	Inlet Duct Outer Surface		
12.30	30	Duct Pneumatic Operated Damper / Flap (Rear Side), Pneumatic operated Damper / Flap Gasket Exhaust		
12.31	N/A	Nut bolts and Clamps		
12.32	N/A	Cyclone separator/VTS assembly		
12.33	N/A	Equipment Dryness and Cleanliness		
12.34	N/A	Screws /Bolts for Corrosion		

12.0	Photo Sr. No.	Component / Area of Inspection	Production	QA
			Observation (Yes /No/NA)	Observation (Yes /No/NA
12.35	N/A	Discoloration OR Stains of Previous Product		
12.36	N/A	Check the locations at which two different materials of construction comes together, for e.g. Stainless steel and view glass, curved surfaces, grooves of gasket are free from the traces /residue of previous product		
Inspection Satisfactory / Not Satisfactory*				
Sign/Date				

*Proceed for next step if visual inspection found “Satisfactory” by Production and QA.

*If visual inspection found “Not Satisfactory” by production, perform the re cleaning and document the cleaning step and Initiate the deviation if found “Not Satisfactory” by QA.

Next Product	Batch No.	Sign/Date

Assemble the machine after Line clearance as per SOP XXXX

Sr. No.	Cleaning Steps	Status (Yes /No /NA)
13.0	**Assembling:**	
13.1	**Expansion Chamber:** Assemble the dismantled gaskets on finger bag fixing ring, Spraygun port and charging assembly	
13.2	**Product Container Bowls**: Assemble the Base plate, Dutch mesh assembly, sampling bottle, charging and discharging assembly.	
13.3	**Lower Plenum:** Close the Inlet air duct flap through selector switch provided on HMI/MMI/IPC panel.	

Assemble the machine after Line clearance as per SOP XXXX

Sr. No.	Cleaning Steps	Status (Yes /No /NA)
13.4	**Spray Gun Assembling** Assemble the spray gun cylinder, Spray gun, nozzles, O-rings and its accessories. **(Applicable for Top Spray Arrangement only)**	
13.5	**Spray Gun Assembling** Assemble the Mini Column, spray gun cylinder, Spray gun, nozzles, O-rings and its accessories. **(Applicable for Bottom Spray Arrangement only)**	
13.6	**Cyclone Separator or Product Conveying System** Assemble the Charging and Discharge assembly and its bag, clamps.	
Done By (Sign/Date):		

Example of Cleaning Procedure of Fluid Bed Dryer and Fluid bed processor

Pictorial Visual Inspection Check Points for FBD/FBP

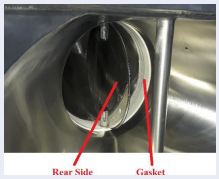
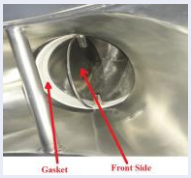
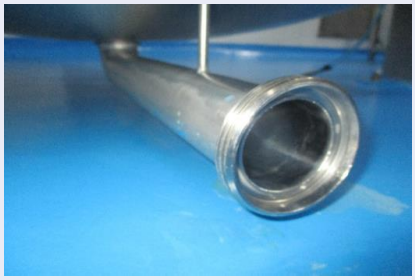
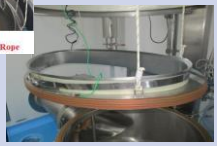
Photo Sr. No.	Component Name	Area of Inspection
01	Lower Plenum/ Plenum Rim	
02	Inlet Duct Flap with Gasket	 
03	Drain Hole	
04	Drain Pipe	
05	Filter Bag Holding Assembly	 FBD Bag holding Assembly  Wruster Bag holding Assembly

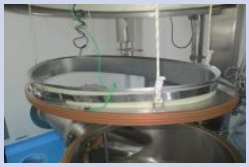
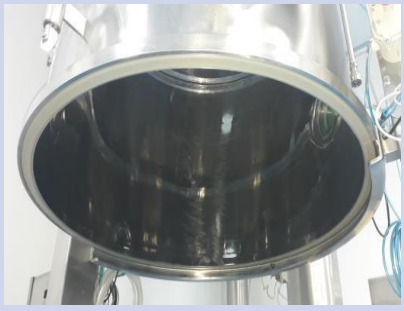
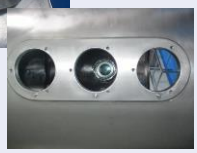
Photo Sr. No.	Component Name	Area of Inspection
06	Gasket –Filter Bag Ring Assembly	 
07	SS Belt for Filter Bag tightening	
08	Expansion Chamber	
09	Spray Gun Port	 
10	Material Charging Port –Expansion Chamber	

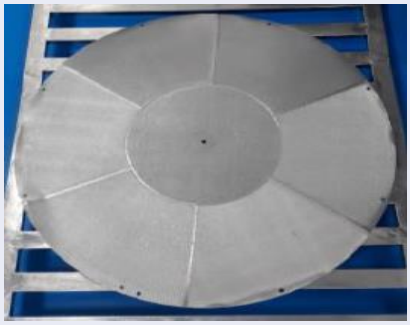
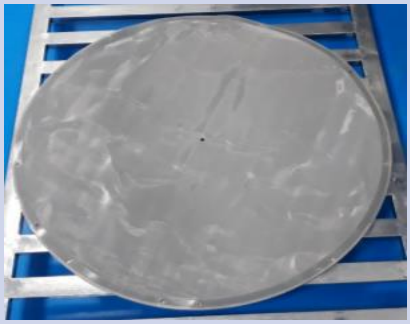
Photo Sr. No.	Component Name	Area of Inspection
11	Product Container Bowl	
12	Sampling Port with Triclover	
13	Holding Clamps to Dutch Mesh & Holding Plate	
14	Dutch Weave Holding Plate	
15	Dutch Weave Mesh	

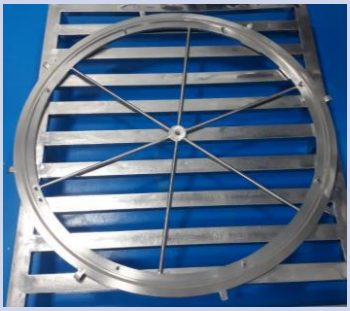
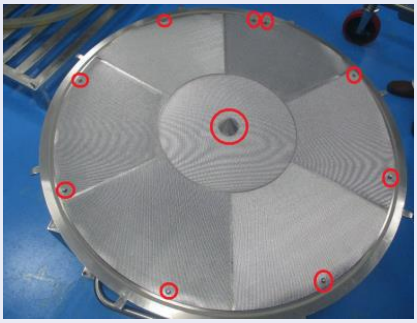
Photo Sr. No.	Component Name	Area of Inspection
16	Dutch Weave Holding Support Cross	
17	Nuts to fit Mesh & Holding Plate to Bowl Rim	
18	View Glass(es) & its Gaskets	 
19	Product Temperature Sensor Port	
20	Product Temperature Sensor	

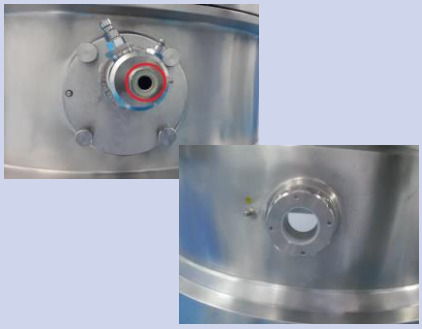
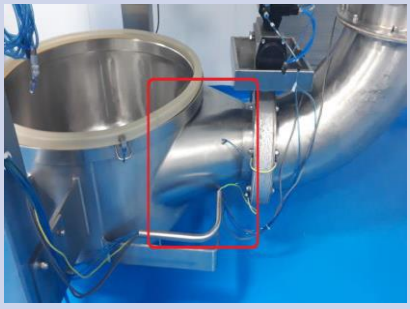
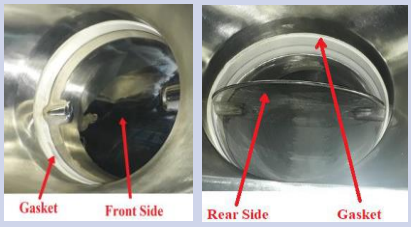
Photo Sr. No.	Component Name	Area of Inspection
21	Material Discharging Port –Product Bowl	
22	Flameproof Lamp	
23	Peristaltic Pump & Manifold	
24	Spray Gun & Nozzle Assembly	
25	Gasket (O-Ring) -Spray Gun & Nozzle Assembly	

Photo Sr. No.	Component Name	Area of Inspection
26	Inflatable Sealing Gaskets	
27	Exhaust Duct Outer Surface	
28	Portion Segment connected between Lower Plenum till Damper / Pneumatic Operated Flap	
29	Inlet Duct Outer Surface	
30	Duct Pneumatic Operated Damper / Flap (Rear Side), Pneumatic operated Damper / Flap Gasket Exhaust	

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