1.0 Purpose

The purpose of this procedure is to describe the processes used for validation and routine execution of methods used for screening of surface allergens, cleaning agent residues, and product residues following cleaning of production equipment.

2.0 Scope

This procedure applies to all cleaning verification and validation activity associated with manufacturing processes. This procedure outlines the overall process to conduct necessary activities under protocol. This procedure includes the evaluation of test cleaning verification test methods for suitability of the test for the intended purpose as well as the application of verification methods to validate a cleaning process.

3.0 Responsibility

3.1 It is the responsibility of QC Management to implement and maintain this procedure.

3.2 It is the responsibility of QC Management and R&D Management to ensure that this procedure is followed.

3.3 It is the responsibility of QC Chemists and R&D personnel to execute validation and verification activities.

4.0 References

4.1 C-105, SOP, Protocol and Report Documentation Requirements

4.2 D-103, SOP, Analytical Method Validation and Verification

4.3 D-111, SOP, Allergen Testing for Production Equipment

4.4 D-116, SOP, ATP Testing for Production Equipment

4.5 MV-LAB-14-017, Protocol, Validation of Allergen Test Methods

4.6 A risk Based Approach to Cleaning Validation using Visible Residue Limits by Richard J. Forsyth and Jeffery L. Harman published in Pharmaceutical Engineering May/June 2008

4.7 Introduction To The ASTM E3106 "Standard Guide To Science-Based AndRisk-Based Cleaning Process Development and Validation" By Andrew Walsh, Thomas Altmann, Joel Bercu, Ph.D., Alfredo Canhoto, Ph.D., David G. Dolan Ph.D., Andreas Flueckiger, M.D., IgorGorsky, Jessica Graham, Ph.D., Ester Lovsin Barle, Ph.D., Ovais Mohammad, Mariann Neverovitch, and Osamu Shirokizawa Published in Pharmaceutical Online June 5 2020

4.8 Replacing the MAC/MACO With The MSC: Rethinking How Cleaning Validation Limits Are Calculated, By By Andrew Walsh; Thomas Altmann; Ralph Basile; Joel Bercu, Ph.D.; Alfredo Canhoto, Ph.D.; Andreas Flueckiger, M.D.; Igor Gorsky;Jessica Graham, Ph.D.; Ester Lovsin Barle, Ph.D.; Ovais Mohammad; Mariann Neverovitch; Siegfried Schmitt, Ph.D.; and OsamuShirokizawa published in Outsourced Pharma August 31, 2022

5.0 Definitions

5.1 **USP** – United States Pharmacopeia

5.2 **AOAC** – Association of Analytical Communities

5.3 **BAM** – Bacteriological Analytical Manual

5.4 **LOM** – Limit of Measure (Sensitivity with accuracy and precision)

5.5 **LOD** – Limit of Detection (Absolute sensitivity)

5.6 **QC** – Quality Control

5.7 **R&D** – Research and Development

5.8 **CIP** – Clean in Place

6.0 Procedure

6.1 Process Overview

6.1.1 Cleaning processes are divided into two categories.

6.1.1.1 Manual cleaning processes are typically not validated. Manual cleaning processes are typically verified after every clean. It is acceptable to validate a manual cleaning process; however, verification is preferred unless the manual cleaning process is very consistent.

6.1.1.2 Automated cleaning processes must be validated unless verified after every clean. Automated cleaning processes include CIP systems.

6.1.2 Test methods used for verification and/or validation of cleaning processes must be suitable for the intended purpose. Test methods used for this purpose must detect analytes of interest at levels associated with acceptable residual limits. Validation and Verification of each specific test method is covered by SOP D-103 Analytical Method Validation and Verification.

6.1.3 Cleaning Validation is defined and documented through protocols and reports. Requirements for protocols and reports are covered by SOP C-105 Protocol and Report Documentation Requirements. The following parameters are typically used in a cleaning validation protocol. Protocols may use alternate approaches as justified in the protocol.

6.1.3.1 The cleaning process must be well defined and documented. If the cleaning process is altered, the cleaning validation should be repeated.

Adding detail to the cleaning method does not necessarily indicate alteration.

6.1.3.2 Limits for analytes of interest are defined. Limits should be based on safety and risk assessment which should be discussed in the protocol.

6.1.3.3 Sample collection methods are defined.

6.1.3.4 Testing methods are defined. Testing methods should be suitable for the intended purpose as discussed above.

6.1.3.5 Execution of cleaning with protocol-defined verification testing is repeated at least three (3) times successfully without intermittent failures.

6.1.4 Cleaning validation may include matrix approaches to include best-case / worst-case scenarios. Best-case / worst-case scenarios may be determined by solubility, identified risks, identified detectability, etc. Matrix approaches are defined and justified in protocols / reports applicable to the cleaning process.

6.2 Verification of Cleaning

6.2.1 Verification of cleaning is the process of inspection, sampling, and/or testing to determine that equipment is satisfactorily clean. Cleaning verification is used after every clean for cleaning processes which are not validated. Cleaning verification is used during cleaning validation protocols to determine success or failure of that validation protocol. Various cleaning verification methods are available and the choice of which methods are used is dependent upon the nature of the analyte of concern.

6.2.2 Verification typically includes visual inspection, ATP swabs, and if known-allergens are present in the previous product, verification includes allergen swabs.

6.2.3 For high potent compounds (i.e. Active Pharmaceutical Ingredients - API)

verification may include the use of analytical methods specific to a particular API or other compound of interest.

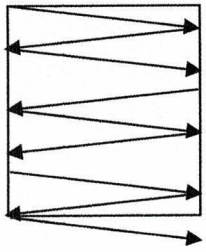
6.3 Swab and Flush Sample Collection

6.3.1 Some test kits contain swabs as part of the test kit. Where specific instructions are available to a test kit, those instructions supersede the instructions provide here.

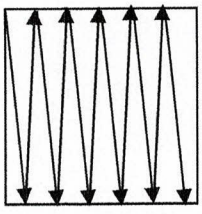
6.3.2 Select a swab suitable for the intended purpose.

6.3.3 For samples generated by swab, a 10cm X 10cm surface area will be swabbed in one direction using one side of the swab. The swab will then be turned over and the surface swabbed in a 90° direction from the first. When obtaining a sample from a hard to clean surface or convoluted surface approximate $100cm^2$ as your sample area. Other sized surface areas can be used with proper scientific justification.

Example of swab technique:



Swab Front-side



Swab Back-side

6.3.4 For areas unreachable by swab, flushing with a fixed quantity of rinse agent (typically water) can be performed. The rinse volume should be a quantity that allows sufficient sensitivity for the surface area tested.

6.3.5 A suitable number of test samples will be taken to effectively demonstrate that

the piece of equipment is residue free.

6.3.5.1 The sampling should be from surfaces that come into contact with the finished product material but other surfaces are acceptable to ensure complete cleaning.

6.3.5.2 If multiple surface types exist at least one representative sample from each surface type must be taken.

6.3.5.3 If corners, edges, channels or other hard to clean areas come in contact with finished product material at least one hard to clean area must be included in the sampling process.

7.0 Revision History

Revision	Date	Description of Changes	CCR	By
0	03/27/14	New	14-0276	B. Johns
1	09/16/16	Change title. Expand SOP to cover validation / verification of cleaning processes for dietary, cosmetics and pharmaceuticals.	16-0824	B. Johns
2	11/27/19	Clarify scope and purpose. Update responsibilities. Add reference to allergen test validation. Update to be consistent with current practices.	19-0908	S. Sassman
3	11/04/23	Update responsibilities, references, logo, title, definitions, and format. Split procedure to define requirements for both verification and validation processes. Remove redundant information.	CC-23-0541	D. Herd