1.1.1. Validation

This area is responsible for training in the use of this SOP, document preparation and testing requirements for particular projects. Provide instruction on specific test procedures and written test protocols. Develop and implement relevant testing templates and calculation spreadsheets. For large validation projects provide a testing and documentation resource to complete the validation activities.

1.1.2. Quality Assurance (QA Manager or Validation Manager)

Review and authorisation of documentation associated with cleaning validation.

1.1.3. Engineering (Projects)

Review and checking documentation associated with cleaning validation. Engineering is responsible for design, installation, and commission and in some projects validation of new and modified cleaning equipment processes. Systems include but are not limited to: product transfer pipework, mixing vessels. Initiating changes to current cleaning processes and procedures by initiation of change requests.

1.1.4. Operations

Initiating changes to current cleaning processes and procedures by initiation of change requests. Review of validation plans and validation test protocols. Provide resource assistance to the specific cleaning validation tasks such as running collecting swab and rinse samples, removal of complex equipment components.

1.1.5. Laboratory

Provide validated Analytical test methods for accurate product residue detection, including swab and rinse surface recovery data. Perform Analytical testing of swab and rinse samples collected during validation using validated procedures. Review and approve Analytical test methods and results, provide documented test results to relevant departments. Review sampling procedures and acceptance criteria for bioburden sampling after cleaning. Perform analysis of bioburden samples and report results

.

2. Types of Cleaning Process and Cleaning Agents

2.1. Manual Cleaning

Effective manual cleaning practices must be established by focusing on the following two areas:

2.1.1. Standard Operating Procedures (SOP)

SOPs will be developed during the Operational Qualification phase of the project. This will be outlined as part of the Validation Plan. If consistently unacceptable or erratic results are obtained the SOP should be considered one of the possible problems and modifications to the procedure may be required. Procedures must be written in a manner, which prevents variation between operators.

2.1.2. Operator Training

Operators must be suitably trained in the use of the manual cleaning SOP.

2.2. Automatic Cleaning In Place (CIP)

SF = safety factor = 1000. This is based on biological activity levels of 1/1000 of the normal active concentration.

Example Calculation

$$MAC = \frac{0.25mg \times 200{,}000mL}{1000 \times 2.0mL} = 25.0\ mg$$

Therefore the total quantity of residual product allowable in a subsequent production batch is 25.0 mg.

3.6.4. Calculating Acceptance Limits For Swabs

1. Take the calculated MAC for the product and divide this number by the total internal surface area of the total product processing system, i.e. preparation and holding vessels + pipework + filling machine. This figure is the amount of residue allowed throughout the entire process, the assumption being that there is even distribution of product residue throughout the process equipment.
2. Example calculation:

   The allowed residue in the entire process = MAC/total surface area

   = 25.0mg/56715 cm^2

   = 0.00044 mg/cm^2 (MAC/cm^2)

   The overall surface area is derived from the following (only as example):

   .

EQUIPMENT/S	EQUIPMENT INTERNAL SURFACE AREA (cm^2)
Mixing tank	26745
Holding tank	26745
Transfer lines	965
Filling Machine	2260
Total	**56715**

This calculated value determines the amount of residual product allowed to remain on 1 square centimetre of the equipment after cleaning. This value is then multiplied by the area to be swabbed to give the allowed limit per swab sample.

If swabbing a 10 cm x10 cm (100 cm^2) surface area and placing the swab in 25.0ml of swabbing solution then the following applies:

$$\textbf{Limit for swab sample} = \frac{MAC/cm^2 \times \text{Swab area}}{\text{Volume of Swab Solution}}$$

$$= \frac{0.00044\ mg/cm^2 \times 100\ cm^2}{25.0\ ml} = 0.0088\ mg/mL\ (8.8\mu g/ml \text{ or ppm per swab})$$

In this case, swab sample results for 100 cm^2 must be $\leq$ 8.8 μg/mL of active to prove that the cleaning process is satisfactory. The value 0.00044 mg/cm^2 was derived from the MAC allowed per swab calculation above.

3.6.5. Calculating Acceptance Limits For Rinse Samples

1. Calculating required rinse volume:

5.5.1. Swab sampling

The swab method should be based on the procedure validated by the analytical laboratory. In many cases the surface of production equipment will not be a flat stainless steel surface. Therefore the swab must be done as close as practically possible to the validated swab procedure.

Non-standard swab areas

Where it is not possible to swab 100cm^2 the actual area swabbed is recorded and an adjustment to the acceptance limit is made. For example, if the swab area is only 50cm^2 the limit is halved.

5.5.2. Rinse sampling

The rinse method should be based on the procedure validated by the Analytical laboratory.

Non-standard rinse volumes

Where it is not possible to rinse to the required ratio of Rinse:Surface area, the actual volume used is recorded and an adjustment to the acceptance limit is made. For example, if the rinse volume calculated is 1L and 2L was required the limit is then halved.

5.6. Monitoring During Automated Cleaning Cycle

The main data required from any test is cleaning water flowrates, cleaning time and water temperatures.

5.7. Collecting Rinse Samples

In some cases for each rinse sample both a chemical and microbiological sample is required, if this is the case collect the microbiological sample 1st then aseptically transfer some of the solution into a sample container for chemical testing.

For manual rinse samples the following precautions should be followed. Containers for collecting samples i.e. sample jars, trays, buckets, etc. must be clean and thoroughly rinsed with distilled water, especially when taking conductivity measurements and for TOC analysis. For TOC testing use clean TOC vials or glass Schott bottles. Any devices such as manual valves used to collect samples must be of a cleanable design and always cleaned prior to use. Containers used to pressure transfer water samples through product lines must also be clean and rinsed thoroughly with Distilled water. For TOC testing it is important to collect a small sample of the rinse water used as a blank sample to measure the background TOC.

5.8. Collecting Swab samples

The principles explained under rinse samples also apply to swab sampling. The swabbing procedure must be based on the procedure validated as part of the analytical method validation. The relevant file for method validation should be used as a basis for describing the swabbing procedure in the test protocol.

5.9. Collecting Microbiological samples (bioburden)

The main requirements are that sample containers are pre-sterilised; the sample valves used are clean and pre-sanitised by flushing with 80°C distilled water for 5 minutes.

5.10. Failed Results

Any failures of the rinse and swab samples must be dealt with by investigating the reasons for the failure; making changes to procedures and then repeating the test. Sampling, testing, re-sampling and re-testing the same equipment should not be conducted if test results

