Standard Operating Procedure

Title: Cleaning Validation Master Plan – Non Sterile Solid

Department	Validation/Technical Services		Document no	VAL-215	
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2 Responsibilities

Responsibilities \ Department	Validation Manager	Validation	Engineering Manager	Engineering	Production Manager	Production	QC Manager	QC Laboratory	Development Manager	Development	Quality Manager	Quality Assurance
Validation study design	P	P	I	I	I	I	I	I	I	I	I	I
Identifying and providing the appropriate level of resource in order to execute the cleaning validation exercises	P	P	(P)		(P)		(P)		(P)		(P)	
Identification of process equipment trains and selection of worst case products for validation	P/A	P	I	I	I	I	I	I	I	I	I/A	I
Calculation of cleaning limits for equipment / processes	P/A	P		I	I	I					A	I
Training of Operators in Cleaning SOPs	I	I			P	P						
Writing and execution of protocols	P/A	P	I	I	A/I	I	I	I	I	I	A/I	I
Review of QC results and final report writing	P/A	P			A						A	
Rinse and Swab Sampling	P	P		I		I	A	I				
Conduct analytical test method validation	(P)/A/I	(P)					P/A/I	P			A/I	
Testing of swab and rinse samples	(P)	I/(P)			I	I	A/P	P				
Validation cleaning studies discrepancy resolution	P/A	P	I	I	I	I	I	I	I	I	A/I	A/I
Update of this CVMP when required	P	P	I		A/I		I		I		A/I	

Where A = Approver P = Primary Ownership (P) = Joint Ownership I = Input

- Time, temperature, flow rates, pressures, volumes for cleaning or soak cycles (and technique for manually cleaned systems)
- Time, temperature, flow rates, pressures, volumes for rinse cycles
- Sequence of cleaning, soak and rinse cycles or steps
- Additional Operating Instructions
- Routine data, samples to be collected during normal operation, including any end of cycle analytical samples
- Assay methods for sample testing
- Maximum hold time after cleaning – Clean Hold Time

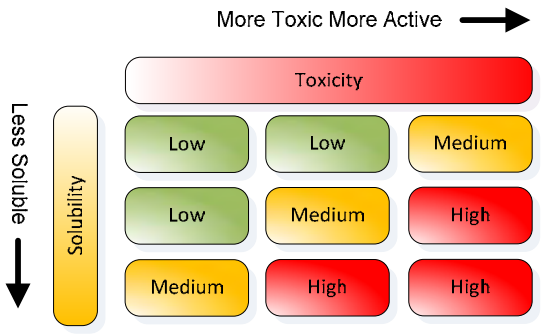
3.4 Risk Based Approach

3.5 Selection of "Worst Case" - Product Bracketing Strategy

3.5.1 A risk-based matrix approach will be used to determine the worst-case product for each cleaning procedure. Cleaning validation will be performed for all equipment cleaning procedures associated with that worst-case (highest risk) product. Acceptable validation of a cleaning procedure for the worst-case product shall constitute validation for all other products that utilise the same cleaning procedure. Cleaning validation will be performed on additional products, as necessary, to verify performance of any cleaning procedures relating to equipment, which was not utilized during the manufacture of the worst-case product.

3.5.2 The risk-based matrix takes into account the following factors (refer Diagram "Risk Matrix"):

- **Solubility** – solubility of the active ingredients in water, as noted in the Merck Index.
- **Toxicity and Concentration – either** based on available toxicology information or based on LD50 Oral (rat) - the amount of a substance required to kill half a given population and percentage of the active ingredients in the formulation residue.



3.5.3 Carry- over calculations for the permissible residue quantities will be based upon available toxicology information for the identified substance(s) of greatest toxicity, highest potency or suitability as in indicating agent for common production equipment.

3.5.4 Swab analysis will generally be performed using the most difficult to remove active drug substance or the most toxic substance, whichever is determined to be of greatest cross-contamination risk. The most difficult to remove substance must be identified based on a combination of solubility in the cleaning agent, and also on first hand experience. In instances where the most potent active used to calculate the acceptance is potentially harmful as a contaminant in other products, swabbing for residues of this active will be conducted as well as on the identified worst case (most difficult to clean active) as an added precaution.

3.5.5 Where swabbing is performed on a worst case active, the acceptance criteria will still be based on the most potent active, not the active being swabbed. This combination provides a high level of

The microbiological acceptance criteria for Total Plate Count (TPC) is based on a maximum allowable count of 1/cm^2 as for swabs and expressed as maximum count per 100mL for each sampling point.

TPC	≤ 1 cfu / cm^2
Pseudomonas spp:	Not Detected/ 100ml
Coliforms:	Not Detected/ 100ml
E.coli:	Not Detected/ swab
Salmonella spp	Not Detected/ swab

Swabs	
TPC:	≤ 1 cfu / cm^2
Yeast & Mould:	≤ 1 cfu / cm^2
Pseudomonas spp.:	Not Detected/ swab
Coliforms:	Not Detected/ swab
E.coli:	Not Detected/ swab
Salmonella spp	Not Detected/ swab

The target limits shall be:

a) Less than, or equal to, 1 cfu per cm2 for product contact surfaces.

b) Absence of E. coli., mould, yeast

3.9 Priority, Schedules and Documentation

3.9.1.1 Schedules for equipment cleaning validation must be based on the following priority:

- Assessment of all new products before initial manufacture (refer Part 3 above)
- Product or product groups assessed as having a high clean ability risk
- Product or product groups assessed as having a medium clean ability risk (if required)
- Product or product groups assessed as having a low clean ability risk (if required)

3.9.1.2 Schedules must be prepared listing line/equipment (groups) train, product(s) or product group(s), and SOP(s) or procedure(s).

3.9.1.3 The following minimum documentation should be available for review on the completion of validation:

- cleaning validation protocol, including location maps of swab sampling
- published cleaning procedure used in the validation
- validation report referenced to raw data
- reference to method validation and active product surface recovery studies

3.10 Cleaning Strategies

Hold times are the times a piece of equipment or system is allowed to remain idle, either after it has been utilised for production processes (dirty-hold time) or after an equipment or system has been cleaned (clean hold-time).

3.11 Clean Hold Time

Clean hold times are the maximum time a piece of equipment or systems are allowed to remain idle between the end of the cleaning process and the beginning of usage. The primary concern is with an adverse change in the cleanliness of the equipment over a period of time.

Clean hold times will be evaluated where the equipment or system is considered to be at risk of change of the cleanliness state when left idle for extended periods of time. Equipments or systems have acceptable hold times evaluated via microbiological or chemical testing as appropriate. Where equipment is sterilised prior to use, a validated overkill sterilisation cycle for the equipment or system would be considered sufficient justification to negate the necessity for microbiological evaluation of a hold time. The requirement to conduct

Document / Definition (Definitions may be found in specific documents)	**Purpose**
	The CVMP provides the specific rationale concerning- selection of allowable carry over limits, grouping of products and equipment, rationale for selection of "marker" or exhibit products. It also defines who is responsible.
Cleaning Validation Schedule *(Attached to CVMP)*	The schedule itemises and prioritized the cleaning validation activities and any supporting activities which are required to achieve the cleaning validation program. Schedules usually cover a 2 – 3 year period.
Cleaning Validation Protocol	A document which documents the process of evaluating the effectiveness of a specific cleaning procedure. This protocol is specific to a cleaning procedure, the marker product (representing a group) and the equipment train.
Risk Assessment *(Protocol)*	The risk assessment reviews the risks associated with the cleaning program i.e. what level of cleaning needs to be achieved, toxicity of actives, worse case scenarios of cross contamination potential.
Identification of Equipment Train *(Protocol)*	An assessment of all equipment used during the manufacture of a particular product (or group of products) identifying worse case scenarios and equipment trains.
Clean Limit – Rational for setting Limit	A limit for acceptable level of "clean", which is defined in the cleaning validation protocol, and defined in terms of (a) maximum carryover levels to the next product and (b) allowable residues per unit are of equipment surface.
Validated Analytical Methods	Methods used for cleaning analysis must be appropriately validated i.e. Limit of Quantitation (LOQ) and Limit of Detection (LOD) must be assessed for each analyte and possibly degradant. An assessment of the precision, accuracy and linearity must also be performed at the LOD and LOQ. Pre-requisites to analytical method validation include qualification and calibration of all equipment/lab instruments used in the analysis.
Procedure for Sampling	In order to ensure consistent and reproducible recovery, a procedure for the sampling (be it swabbing, rinse collection or placebo approach) must be written and trained to.
Recovery Studies – Swabbing Protocol	When swabbing is used as a sampling technique, as well as training to the procedure, it is a requirement to perform recovery studies which evaluate the ability of the sampling procedure to recover a specific analyte from specific surfaces. The recovery study is also used to quality the analysts or samplers performing the swab per the protocol.
Qualification of Swabbers	This may be achieved in the above document Recovery Study – Swabbing protocol. Its purpose is to show the effectiveness of training of "swabbers" to take samples in a reliable and reproducible manner.

