Standard Operating Procedure

Title: Cleaning Validation Master Plan – Veterinary Biologicals

Department	Validation/Technical Services		Document no	VAL-220	
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1. Introduction

[***Enter company name***] manufactures and distributes a range of sterile and non-sterile, liquid, veterinary biological and pharmaceutical products from their sites [***address***].

The GMP facility has Code of Good Manufacturing Practice (cGMP) licenses with the **[*List all licenses*]**.

This document aims to summarise the overall intentions and approach to the validation of the cleaning equipment and procedures involved in manufacture of sterile veterinary biologic products for [***Enter company name***].

It is intended to be a working document and will be periodically updated by site management responsible for the execution of validation.

2. Purpose and Scope

The Cleaning Validation Master Plan outlines the cleaning program and the associated cleaning validation strategies performed in the Biologics manufacturing area of the [Enter company name] facility. This document presents the methodology to achieve and demonstrate acceptable standards of cleanliness for equipment coming in contact with product or in-process material.

This document is intended for use as a guidance document for the development of specific plans or protocols for a given cleaning validation effort to be performed at in the Veterinary Biologics area. This document defines the expected methodology and rationales to be applied in those documents.

This cleaning validation master plan will discuss the following:

- Scope of the plan including products and locations
- Cleaning methods including systems and cleaning agents
- Criteria to Establish for Cleaning SOPs
- General Discussion of Cleaning Validation Evaluation and Testing

It will also discuss the Strategies, Approaches and Rationales used in cleaning validation including:

- Worst Case, Bracketing Approach
- Analysis and Acceptance Criteria
- Clean and Dirty Hold Times
- Evaluating Need for Cleaning Validation Studies
- On-going Cleaning Validation Program

4. Rationale and General Principles

4.1 Rationale

Products manufactured in the biologicals/aseptic production facility can be contaminated by other products (cross contamination), by cleaning agents, by micro-organisms or by foreign matter. In a multipurpose facility the same (common) equipment may be used for many different products.

The objective of cleaning validation is to verify the effectiveness of the documented cleaning procedure for removal of product residues, degradation products, excipients and/or cleaning agents so that the analytical monitoring may be reduced to a minimum in the routine phase. In addition it is necessary to assess the risk of equipment usage associated with cross contamination of active ingredients.

4.2 General Principles

The following general principles apply to cleaning validation:

4.2.1 Only cleaning procedures for product contact surfaces are subject to validation. Only cleaning procedures for “product to product” changeover (common equipment) will be fully validated.

4.2.2 Cleaning procedures for products and processes which are very similar do not need to be individually validated. Documented grouping or bracketing of similar products and similar equipment trains is acceptable provided a documented risk assessment is undertaken.

4.2.3 Dedicated equipment is confirmed as visually clean following “same product to same product” cleaning procedures. The verification is documented on the batch record prior to commencing subsequent batches.

4.2.4 Cleaning validation must, where relevant, address removal of cleaning agents and micro-organisms as well as active substances/products.

4.2.5 Where cleaning validation is required, a combination of analytical testing for residues on equipment surfaces, analysis of flush volumes and visual inspection is required. A successful validation must meet the established acceptance criteria.

4.2.6 Equipment cleaning validation may be performed concurrently with actual production steps during process development and clinical manufacturing. Validation programs should be continued through full scale commercial production.

4.2.7 The primary methods of analytical testing will be based on swab analysis (of predefined “worst case” locations) and/or appropriate rinse sampling analysis. It will be assumed that contamination detected will be incorporated into the subsequent batch

4.2.8 Where sampling detects no residues, calculations of residue will assume residues to be at the limit of detection of the test method. This “worst case” value will be used in residue calculations.

4.2.9 Bracketing of products may be used to validate a common cleaning procedure. In such cases, the acceptance criteria and swab analysis will be based on “worst case” combinations as detailed following.

4.2.10 A maximum time between end of use of equipment and cleaning (dirty hold time) should be defined and included in the validation study, or sufficient justification for not conducting such an evaluation based on risk assessment. Similarly, clean hold times should be established for equipment left in a clean state for prolonged periods prior to usage. Items that are sterilised prior to use or utilised within 72 hours of cleaning are generally considered to not require establishment of clean hold-times, unless deemed otherwise during the risk assessment process. Reduced cleaning may be conducted for campaign production modes (Refer to section 10 for further detail).

4.2.11 Analytical methods used to validate cleaning must also be validated at least for recovery levels and limit of detection.

assuming a worst possible case exposure level. The cumulative value will thus over-estimate the maximum possible residue to which a consumer could be exposed.

5.1.8 Justification of worst case active substance and calculation of worst case acceptance criteria should be attached as an appendix to each protocol or conducted utilising PVA-SOP-046.

5.1.9 If the results of the validation exercise fail to meet the acceptance criteria due to the accumulation of several over estimations of potential residue in a “worst case” approach, then the results shall be reviewed to assess if the failure is due to one or more locations with extraordinarily high residue levels. If this is the case, then the applicable cleaning procedures will be revised to ensure l residue levels are achievable and revalidated. If no locations are found to be unusually contaminated, and the failure is attributed to excessive overestimation due to the assumptions made, then the acceptance criteria may be recalculated to reflect actual common surface areas rather than total estimated applicable surface areas.

5.2 Potential Process Residues

Products manufactured in the biologics facility, have similar starting materials and utilise similar processing steps. Due to product commonality, the residue types are similar from product to product. The table below illustrates typical example residue types for products manufactured at [Enter company name].

Potential Residue Type	Example Residues	Potential Detection Methodology
Product	Moxidectin Selenium Thiomersal (Thimerosal) Phenol Protein	Material Specific Assays Total Organic Carbon
Adjuvant	Aluminium (as Hydroxide or Potassium Aluminium Sulphate)	Substance Specific Assays
General	Lipids, Proteins	Visual Inspection Total Organic Carbon
Detergents	Sodium Hydroxide / Sodium Carbonate / Citric Acid	pH/Conductivity, Total Organic Carbon

Specific use and testing residues are identified in the respective cleaning validation protocols.

- number of replications of the validation (normally three episodes are required)
- acceptance criteria (stated permitted exposure limits and equivalent test limit levels)

8.2 The Validation Report should contain the following:

- Individual swab and/or rinse results summaries
- Estimated total contamination, calculated by multiplying swab results by surface area or vice versa
- A statement of acceptability of the cleaning method
- Recommendations for applicable routine monitoring

9. Acceptance Criteria

9.1 Product and Detergent Residues

The product residue limits should also consider the cleaning criteria:

Visual Inspection:

No quantity of residue will be visible on any equipment surface post-cleaning when the equipment is dry.

Product Residues – the most scientifically justifiable residue quantity applicable from following criteria.

(a) A toxicology based calculation. specifically, a heath based exposure limit for residual active substances that pose a cross contamination risk. The limit is termed the Permitted Daily Exposure (PDE)(a unit quantity which is applicable when considering the target patient weight). This quantity varies depending on the available data to support the No-Observable Effect Level (NOEL). The NOEL should be based on available toxicology data.

(b) Where toxicological data is not available, no more than 1/1000th of the minimum therapeutic dose of any product is to be present as a potential contaminant in the maximum allowable daily dose of a subsequent product. (Note: A safety factor of 1/100th may be used for products or product components of less risk with suitable justification (e.g. product intermediates or product intermediates which share common manufacturing equipment which are recombined in the final product)

Permitted Daily Exposure (PDE) or Maximum Acceptable Carry-Over (MACO) Limits

The permitted carry over quantity (of previous product or detergent residues) on common product contact surfaces, may be calculated based on the potential exposure of the target animal subsequently taking the largest allowable daily dose (where toxicological data is not available). For calculation purposes, the worst case should be used, that being a subsequent batch with the least number and/or quantity of maximum daily doses per batch. The carry-over calculations may be applied over the respective equipment, however detergent residues should be considered over the entirety of the manufacturing process where a detergent is utilised on multiple pieces of product contact equipment/systems as part of the manufacturing process. Refer to PVA-SOP-046 for evaluation.

9.1.16 Microbiological Contamination

The requirement for microbial testing shall be determined on a case by case basis and shall be appropriate for the products to be cleaned. Where microbial testing is not required justification shall be made in the validation protocol.

The microbiological acceptance criteria for Total Plate Count (TPC) is based on a maximum allowable count of 4/cm^2 as for swabs and expressed as maximum count per 100mL for each sampling point.

TPC ≤ 4 cfu / cm^2

13. Cleaning Validation Program – Required Documents Table

The following table describes documents (and some important definitions within documents) that together describe the cleaning validation system.

Document / Definition (Definitions may be found in specific documents)	**Purpose**
Cleaning Validation (Master) Plan (CVMP) *This Document*	The cleaning validation plan itemises the specific requirements as defined in regulatory and other guidelines along with an analysis of resources, definition of responsibilities and allocation of responsibilities for the writing of protocols, execution of validation and review of data. 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 – Rationale 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, if required enter into the method validation master plan.
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.

3. New or Modified Product/Process Material

Instruction	Component Description	Component Concentration
List the Excipients in the Product Formulation	1.	
	2.	
	3.	
	4.	
	5.	
	6.	
	7.	
	8.	
	8.	
	10.	
	11.	
	12.	
Attach material data for all Excipients (typically available in the raw material MSDS)	Sign/Date	

4. Enter all product contact equipment in the process list below, in order from commencement of manufacture to the completion.

4.1 MEDIA PREPARATION EQUIPMENT

4.1.1	
4.1.2	
4.1.3	
4.1.4	
4.1.5	
4.1.6	
4.1.7	
4.1.8	
4.1.9	
4.1.10	

4.2 ANTIGEN AREA EQUIPMENT

4.2.1	
4.2.2	
4.2.3	
4.2.4	
4.2.5	
4.2.6	
4.2.7	
4.2.8	
4.2.9	
4.2.10	

