Standard Operating Procedure

Title: Maximum Safe Carry-Over (MSCO) Determination

Department	Validation/Technical Services		Document no	VAL-195	
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A PURPOSE

The purpose of this document is to instruct the user on the operations required in order to conduct a Maximum Safe Carry-Over Determination (MSCO) for a piece of equipment or product equipment grouping.

B SCOPE

The scope of this SOP is limited to instructing the user on how to conduct a MSCO determination, following documented risk assessment of the materials and products to be processed on a piece of equipment or product equipment train.

C RESPONSIBILITY

1 **The Validation Engineer and/or Supervisor** is responsible for obtaining true, compliant data for conducting a Maximum Allowable Carry Over (MACO). They are responsible for following the calculation process as defined in this SOP and for review of the MACO calculations generated by peers.

2 **The Quality Assurance Manager(s) and/or Quality Manager** are responsible for review of the MACO calculations and formal acceptance of the indicated results for reference in future studies.

D PROCESS SPECIFIC INFORMATION

1. Regulations

Regulatory References which govern the actions outlined in this SOP are contained below.

1.1 PIC/S Guide to Good Manufacturing Practice (GMP) - 15 January 2009, PE 009-8.

1.1.1 Guide to Good Manufacturing Practice for Medicinal Products - Part II, Chapter 12: Section 12.7

1.1.2 Guide to Good Manufacturing Practice for Medicinal Products Annexes, Annex 15: Qualification and Validation, Clauses 36 - 42

2. Guidelines

The guidelines utilized for reference for this SOP are included below

2.1 Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (EMA, 2014)

2.2 ICH Topic Q3C (R4) Impurities: Guideline for Residual Solvents (EMA, 2009)

E. BACKGROUND AND CALCULATION INFORMATION

1. Guideline for MSCO Calculation

1.1 The MSCO calculation is derived from the European Medicines Agency (EMA) guidelines for compliance with European Union (EU) GMP regulations regarding cleaning validation. This is required for product which is exported to regions governed by EU GMP regulations. The previous term utilized for calculating residue limits “Maximum Allowable Carry-Over” (MACO) has been replaced with Maximum Safe Carry-Over, owing to the derivation of the value from the Permitted Daily Exposure calculations.

$$NOAEL\ from\ LD_{50} = \frac{LD_{50}\left(\frac{mg}{kg}{day}\right) \times Target\ Animal\ Weight(e.g.\ 50kg\ for\ Sheep)}{2000}$$

6.2.1 It should be noted that this formula (adapted from the "guidance on aspects of cleaning validation inactive pharmaceutical ingredient plants" (APIC, 2000)) should only be utilized where toxicological data has not been found available.

1.3 The use of this equation in place of toxicological assessment data should be considered based on the risk of the target species.

1.4 As an additional alternative, the Low Observed Adverse Effect Level (LOAEL) may be utilized to calculate the NOAEL. The LOAEL can be obtained from the Minimum Therapeutic Dose value (reported in appropriate scientific literature). If the LOAEL is utilized in the PDE calculation, then an F5 factor of 10 must be used (refer to section 2 for greater detail).

2. F – Value Assumptions for PDE

The assumptions for the F-values chosen for calculations are indicated in the sections below. Select the appropriate F – values corresponding to the toxicological data/NOAEL/LOAEL source as described in section F1. Each F-value selection should be justified as per the guidance below or based on the risk of the target species.

2.1 The F1 Factor is for extrapolation of data between (animal) species.

- F1 = 5 for extrapolation from rats to humans
- F1 = 12 for extrapolation from mice to humans
- F1 = 2 for extrapolation from dogs to humans
- F1 = 2.5 for extrapolation from rabbits to humans
- F1 = 3 for extrapolation from monkeys to humans
- F1 = 10 for extrapolation from other animals to humans

2.2 The F2 factor is nominally a factor of 10 to account for variability between individuals

- A factor of 10 is generally given for all organic solvents, and 10 is typically used consistently in guidelines.

2.3 The F3 factor is a variable factor to account for toxicity studies of short-term exposure

- F3 = 1 for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys).
- F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.
- F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents.
- F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents.
- F3 = 10 for studies of a shorter duration. In all cases, the higher factor has been used for study durations between the time points, e.g., a factor of 2 for a 9-month rodent study.

2.4 F4 is a factor that may be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the following factors are used:

- F4 = 1 for fetal toxicity associated with maternal toxicity
- F4 = 5 for fetal toxicity without maternal toxicity F4 = 5 for a teratogenic effect with maternal toxicity

Appendix A: Biologicals Area Cleaning Validation New or Changed Product, Process and Equipment Assessment

1. Introduction

This form is to be utilised for recording new product details and/ new process details that may have impact on the applicability of existing cleaning procedures on the biological production area.

2. Purpose and Scope

This form will be utilised for assessment of new product/process and equipment risk in both blending and antigen production areas. The form will guide the user to supply appropriate product and equipment information so that the impact of the new product material components and process can be assessed in regards to existing or future cleaning validation documentation.

3. New or Modified Product/Process Material

Product Name:_____

Product Type (Circle): Vaccine / Sterile Pharmaceutical / Antigen (Bacterin) / Antigen (Toxoid)

Is the product aqueous or non- aqueous? (Circle): Aqueous / Non - Aqueous

Instruction	Component Description	Component Concentration
List the Active Pharmaceutical Ingredients (APIs) that are of a biological origin.	1.	
	2.	
	3.	
	4.	
	5.	
	6.	
List the Active Pharmaceutical Ingredients (APIs) that are of a chemical origin.	1.	
	2.	
	3.	
	4.	
	5.	
	6.	
Attach the Product Formulation Sheet or the Finished Product Specification containing the product component specifications	Sign/Date	
Attach Solubility Data for all APIs (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	

