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Review on Selection of Worst Case Product for Cleaning Validation

Ashwini Mahajan*

Department of Pharmaceutics, Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda, Dist- Jalgaon, Maharashtra, India

Review Article

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***For Correspondence**

Ashwini Mahajan, Department of Pharmaceutics, Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda, Dist- Jalgaon, Maharashtra, India

E-mail: ashwini.mahajan8@gmail.com

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ABSTRACT

The main purpose of cleaning validation is to prove the effectiveness and consistency of cleaning in a given pharmaceutical production equipment to prevent cross contamination and adulteration of drug products with other active ingredients like unintended compounds or microbiological contamination leads to prevent several serious problems and also useful in related studies like packaging component cleaning validation. So it is necessary to select the worst case product and validate it, different techniques are used to select the worst case product, solubility, cleanability, potency, probability of batches of the product. MACO calculation.

INTRODUCTION

Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning pharmaceutical production equipment. Validations of equipment cleaning procedures are mainly used in pharmaceutical industries to prevent cross contamination and adulteration of drug products hence is critically important 2. The prime purpose of validating a cleaning process is to ensure compliance with federal and other standard regulations. The most important benefit of conducting such a validation work is the identification and correction of potential problems previously unsuspected, which could compromise the safety, efficacy or quality of subsequent batches of drug product produced within the equipment. This paper provides a review of the current trends in cleaning validation and its related importance [1].

OBJECTIVE

The objective of this study is to recommend an approach to review and evaluate pharmacological and toxicological data of individual active substances and thus enable determination of threshold levels as referred to in the GMP guideline. These levels can be used as a risk identification tool and can also be used to justify carry over limits used in cleaning validation. Deviation from the main approach highlighted in this guideline to derive safe threshold levels could be accepted if adequately justified [2,3].

METHODS of CALCULATING ACCEPTANCE CRITERIA

Acceptance criteria using health-based data

The Maximum Allowable Carryover (MACO) should be based upon the Acceptable Daily Exposure (ADE) when this data is available. The principle of MACO calculation is that you calculate your acceptable carry-over of your previous product, based upon the ADE, into your next product.

Procedure: Calculate the ADE (Acceptable Daily Exposure) according to the following equation and use the result for the calculation of the MACO.

$$\mathrm{ADE} = \frac{\mathrm{NOAEL} \times \mathrm{BW}}{\mathrm{UFc} \times \mathrm{MF} \times \mathrm{PK}}$$

From the ADE number, a MACO can be calculated according to:

$$\mathrm{MACO} = \frac{\mathrm{ADEprevious} \times \mathrm{MBSnext}}{\mathrm{TDDnext}}$$

MACO: Maximum Allowable Carryover: acceptable transferred amount from the previous product into your next product (mg).

ADE: Acceptable Daily Exposure (mg/day).

NOAEL: No Observed Adverse Effect Level (mg/kg/day).

BW: Is the weight of an average adult (e.g. 70 kg).

UFc: Composite Uncertainty Factor: combination of factors which reflects the inter- individual variability, interspecies differences, sub-chronic-to-chronic extrapolation, LOEL-to-NOEL extrapolation, database completeness.

MF: Modifying Factor: a factor to address uncertainties not covered by the other factors.

PK: Pharmacokinetic Adjustments.

TDDnext: Standard Therapeutic Daily Dose for the next product (mg/day).

MBSnext: Minimum batch size for the next product(s) (where MACO can end up) (mg).

The PDE uses the no observed effect level (NOEL) instead of the no observed adverse effect level (NOAEL) used in the ADE calculation. The PDE may also be used as alternative to the ADE to calculate the MACO. Instead of calculating each potential product change situation, the worst case scenario can be chosen. Then a case with most active API (lowest ADE) is chosen to end up in the following API with the smallest ratio of batch size divided with TDD (MBS/TDD ratio). If OEL data is available, the ADE can be derived from the OEL.

Acceptance criteria based on therapeutic daily dose

When limited toxicity data is available and the Therapeutic Daily Dose (TDD) is known, this calculation may be used. It is used for final product changeover API Process A to API Process B.

Procedure: Establish the limit for Maximum Allowable Carryover (MACO) according to the following equation.

$$\mathrm{MACO} = \frac{\mathrm{TDDprevious} \times \mathrm{MBSnext}}{\mathrm{SF} \times \mathrm{TDDnext}}$$

Acceptance criteria based on LD50

In cases where no other data is available (e.g. ADE, OEL, TDD,…) and only LD50 data is available (e.g. chemicals, intermediates, detergents, …), the MACO can be based upon LD50 data.

Procedure: Calculate the so called NOEL number (No Observable Effect Level) according to the following equation and use the result for the establishment of MACO (See [3] oe page 53 - for reference).

$$\mathrm{NOEL} = \frac{\mathrm{LD50} \times \mathrm{BW}}{2000}$$

From the NOEL number a MACO can be calculated according to:

$$\mathrm{MACO} = \frac{\mathrm{NOELprevious} \times \mathrm{MBSnext}}{\mathrm{SFnext} \times \mathrm{TDDnext}}$$

MACO: Maximum Allowance Carryover: acceptable transferred amount from the previous product into your next product (mg).

NOEL: previous No Observed Effect Level (mg/day).

LD50: Lethal Dose 50 in mg/kg animal. The identification of the animal (mouse, rat etc.) and the way of entry (IV, oral etc.) is important (mg/kg).

BW Is the weight of an average adult (e.g. 70 kg) (kg)

2000 is an empirical constant

TDDnext: Standard Therapeutic Daily Dose for the next product (mg/day).

MBSnext: Minimum batch size for the next product (s) (where MACO can end up).

SFnext: Safety factor.

The safety factor (SF) varies depending on the route of administration (see below). Generally a factor of 200 is employed when manufacturing APIs to be administered in oral dosage forms (Table 1).

Table 1. Manufacturing APIs to be administered in oral dosage forms.

Safety factors: Topicals	Oral products	Parenterals
10 – 100	100 – 1000	1000 – 10 000

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Bracketing and worst case rating

Introduction: The cleaning processes of multiple product use equipment in API facilities are subject to requirements for cleaning validation. The validation effort could be huge. In order to minimize the amount of validation required, a worst case approach for the validation can be used. By means of a bracketing procedure the substances are grouped. A worst case rating procedure is used to select the worst case in each group.

Validation of the worst case situation takes place. However, it is of utmost importance that a documented scientific rational for the chosen worst cases exists. This chapter gives an overview of the suggested work to be carried out, the acceptance criteria and the methodology for evaluation of the data. It should be emphasized that this is only an example to give guidance. The equipment, the substances produced and the procedures in place may vary; and this results in other solutions than those given in this example. The worst case rating priority will then support a conclusion that the cleaning procedures are effective for all drug substances and other chemicals within the bracket, including those not individually tested.

Bracketing procedure: The objective of a bracketing project is for the company to demonstrate that it has a scientific rationale for its worst case rating of the substances in the cleaning validation program. The first thing to do is to make groups and sub groups - which we will term "bracketing", from which worst cases will later be selected based on the results from threating. The bracketing procedure should be included in a company policy, or an SOP or an equivalent document on cleaning validation. A multipurpose facility, Clean Company, is presented as an example we will follow.

Equipment train: The Clean Company is a multipurpose site for synthesis and isolation of organic substances (Figure 1). It is divided into six equipment trains separated from each other and intended for different use (earlier API steps, final API purification, drying etc.). In Train A 9 substances can be produced, in Train B 9 substances can be produced, in Train C 8 substances can be produced, in Train D 8 substances can be produced, in Train E 10 substances can be produced, and in Train F 11 substances can be produced. With no bracketing and worst case rating, cleaning validation studies would be required for each of the 55 substances.

The first grouping criterion is that the substances in a group are produced in identical equipment trains and cleaned out following the same cleaning procedure/SOP. The ideal with regard to cleaning validation (as will be discussed in 7.3) each train could be considered as a group. Then 6 worst cases would ideally be identified. In reality, the number of worst cases identified will often be something between these two extremes (more than 6, but less than 55). Clean Company.

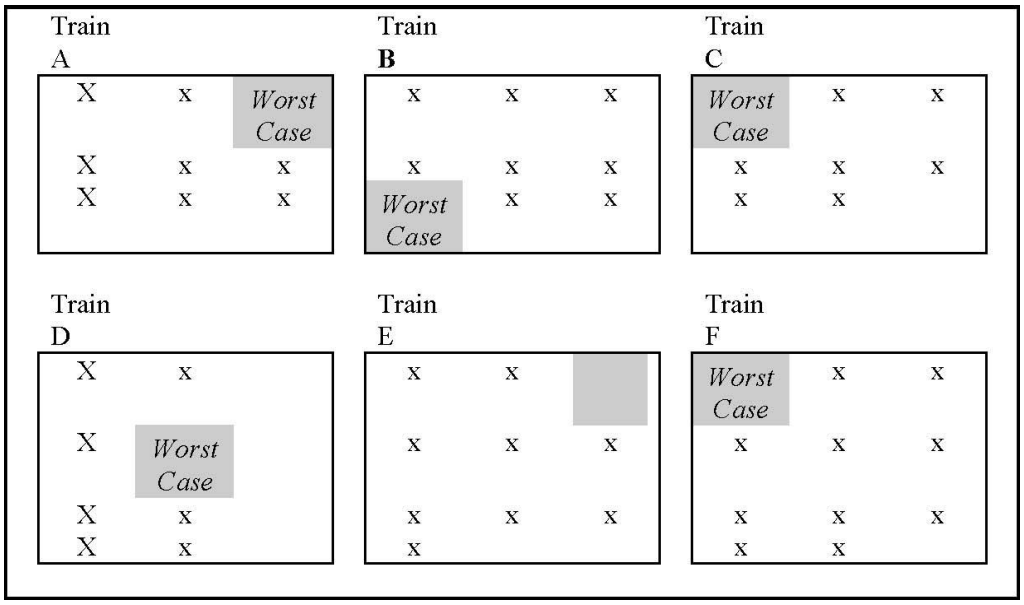

Figure 1. Clean Company's ideal example (1 train considered as 1 group) gives 6 worst cases.

In this example the main classes in this bracketing are based on the different Trains. The following equipment classes are maintained:

- Train A
- Train B
- Train C
- Train D
- Train E
- Train F

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Investigations and Worst Case Rating (Wcr)/risk assessment

A worst case rating study/Risk assessment will priorities existing drug substances, in a cleaning validation program, based on information on applicable criteria chosen by the company. Clean company chose the following criteria which are relevant to the molecule preparation in their facility (companies should evaluate individual situations):

- a) Hardest to clean: experience from production; b) Solubility in used solvent; c) Lowest Acceptable Daily Exposure(If ADE data are not available, other pharmacological (dose), OEL or toxicity data (LD50) may be used (see chapter 4); d) Lowest therapeutic dose (or toxicity data LD50).
- In order to present documented evidence supporting the scientific rating for each criterion, investigations (a formalized Risk assessment) should be carried out and formal reports should be written. For each criterion groups of rating with corresponding descriptive terms should be presented. When available, the descriptive terms can be chosen from the scientific literature on the subject (i. e. for solubility and toxicity). For other cases the rating is based on scientific investigations carried out by the company and collecting experience regarding details on the cleaning processes (i.e. "experience from production").
- Clean Company chose to execute the WCR according to a formal protocol, in which the rating system was identified and the rating documented. In a Risk assessment report the results including the WCR were summarized, as well as conclusions [4-7].

Hardest to clean out - experience from production: One criterion which can be used is, experience from production with regard to how difficult a substance is to clean out. The study is recommended to be in the form of interviews with operators and supervisors. A standardized sheet with questions could be used in which the answers are noted. Hard-to-clean substances are identified and the difficulty of cleaning could be rated according to the three categories suggested below. The opinions of the personnel are subjective, and therefore should be supported by a scientific rationale (Table 2).

Category: 1 = Easy 2 = Medium 3 = Difficult

Table 2. Hardest to Clean out - Experience from Production.

PDE Value	Rating
>500 mcg	1
100- 500 mcg	2
10-99 mcg	3
1-9 mcg	4
<1 mcg	5

Solubility: A solubility-rating should be carried out based on the solubility of the substances in the solvents used for cleaning. Suggested rating numbers, with explanations, are presented in Table 3 below.

Table 3. Solubility rating.

Solubility (from USP)	Solubility factor (Rating)
Very soluble	1
Freely soluble	2
Soluble	3
Sparingly soluble	4
Slightly soluble	5
Very slightly soluble	6
Practically insoluble	7

ADE concept: The Acceptable Daily Exposure defines a limit at which a patient may be exposed every day for a lifetime with acceptable risks related to adverse health effects. An example of rating numbers, with explanations, is presented in the Table 4 below.

Therapeutic doses: An investigation of therapeutic doses is typically base on oral and/or parenteral data. In the cases where the therapeutic doses are not available, corresponding values based on the toxicity could be used (recalculated according to company procedure). An example or rating numbers, with explanations, are presented in Table 4 below.

Table 4. Therapeutic Doses.

Therapeutic Dose	Rating
>100 mg	1
100- 1000 mg	2
10-99 mg	3

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1-9 mg	4
<1 mg	5

Toxicity (LD 50): Shown in Table 5.

Table 5. This table shows toxicity (LD 50).

Drug Toxicity (LD50)	Rating
Above 1000	1
600 to 1000	2
300 to 599	3
100 to 299	4
01 o 99	5

Potency: Shown in Table 6.

Table 6. This table shows Potency.

Normal Daily dose (Potency)	Rating
Above 600 mg	1
400 to 599 mg	2
200 to 399 mg	3
5-199 mg	4
<5 mg	5

Occupation factor: Shown in Table 7.

Table 7. This table shows occupation factor.

Frequency of manufacture (No. of lots/ batches)	Rating
<2	1
4	2
6	3
8	4
>10	5

Worst Case Rating

The substances are scientifically matrixes by equipment class (train/equipment) and cleaning class (procedure). Each existing combination of the classes is considered as a group. When this bracketing has been carried out, the - "Worst Case Rating (WCR)"- can start. For at least one worst case in each group, cleaning validation studies shall be carried out. The rating procedure for Clean Company presented as an example could be used [8-10].

Rating procedure: During a worst case rating, the results of the investigations are summarized for each substance in each equipment class. If the evaluation of the cleaning procedures indicates that some of the substances have unique cleaning procedures, then each of those substances will be considered as a group (with one group member which is the worst case).

The risk assessment rating for each criterion for each product shall be provided into the worst case selection matrix as below. Total ranking shall be calculated by addition of all ratings. The product with the highest value and highest risk in terms of toxicity (PDE) and clean ability will be considered as worst case (Table 8).

Table 8. Product D shall be considered as worst case product.

Product	Ranking						
	Clean-ability	Solubility	PDE	Toxicity (LD 50)	Potency	Occupation Factor	Total
	(1-5)	(1-7)	(1-5)	(1-5)	(1-5)	(1-5)	
A	1	2	3	4	5	5	20
B	2	5	2	1	3	4	17
C	5	5	2	1	3	2	18
D	2	6	4	5	4	3	24
E	1	4	3	4	2	1	15

In case the total ranking of two products is same, than the hardest to clean product shall be considered worst case. If clean ability of the products is also similar, the product with high risk in PDE value shall be considered worst case. If the clean ability and PDE factor are similar for the products, risk shall be assessed serially based upon solubility, toxicity, potency and Occupation factor.

Re-rating: Change control should be applied to the WCR. If the conditions for the rating are changed, then a re-rating procedure should be carried out. The following listing gives examples where a formal re-rating procedure may be required.

- Changed cleaning method
- Changed process
- Changed/additional new product
- Changed/new equipment

After re-rating, it is recommended to issue an official controlled document including a worst case listing or table, with the same type of result presented for the involved substances/ equipment/methods, as for the original rating.

CONCLUSION

In cleaning validation worst case product is selected by using different techniques and that product is validated in related studies like packaging component cleaning validation. So it is necessary to select the worst case product and validate it, different techniques are used to select the worst case product, solubility, cleanability, potency, probability of batches of the product. MACO calculation.

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