Cleaning Validation in Multipurpose Facilities
Implementation of MACO calculation based on PDE approach

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1. Introduction

Production of different medicinal products in shared facilities can lead to potential cross-contamination, which may pose a health risk. To this end, the EMA guideline "*Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"* introduces a new health-based method of determining the maximum acceptable level of carryover (MACO) in shared facilities - the Permitted Daily Exposure (PDE).

Accordingly, this regulatory change aims to standardize the way the MACO calculation in shared facilities is approached, by implementing a health-based, toxicological parameter in detriment of other outdated, unscientific-based methods such as, the 1/1000th of the TDD and the LD_{50}. This science based parameter, the Permitted Daily Exposure, is a toxicological parameter determined through a structured scientific evaluation of all the pharmacological and toxicological data of a particular substance.

EMA's guideline has also drawn the notion that product segregation might not be necessary in the cases where an adequate strategy of health-based exposure limit determination can support product's manufacture in shared facilities. Accordingly, the definition of dedicated facilities is no longer based on product's pharmacological categories but instead, is based upon the outcome of a toxicological/pharmacological evaluation.

2. Purpose

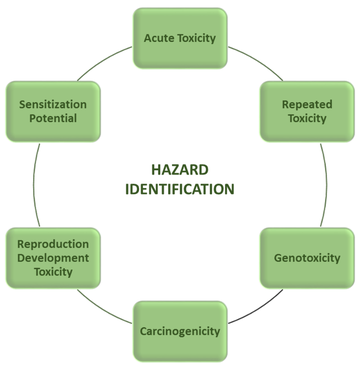
The purpose of the present study was to implement in a multipurpose facility the new health-based methodology of the maximum acceptable level of carryover (MACO) determination, through the following stages:

- PDE determination of all the substances manufactured in the multipurpose facility;
- Implementation of the health-based methodology of MACO determination;
- Evaluation of the impact of the newly introduced methodology in the previously implemented acceptance limits;
- Establishment of a cleaning validation strategy which guarantees the absence of cross-contamination.

3. Methodology

According to the guideline, PDE determination should be carried out through a thorough evaluation of substance's pharmacological and toxicological data, which involves five major steps:

- Hazard identification by reviewing all relevant data;
- Critical effect(s) identification;



- Determination of the no-observed-adverse-effect-level (NOAEL) of the finding(s) identified as critical effect(s);
- Application of the adequate adjustment factors to account for various uncertainties;
- PDE calculation by the formula;

$$PDE = \frac{NOAEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

Where,
PDE = Permitted Daily Exposure (mg/day); NOAEL = No-observed-adverse-effect-level (mg/kgday); F_1-F_5 = Adjustment Factors

- Comparison of the obtained MACO acceptance levels through the implementation of the newly and already introduced, conservative methodologies;

Therapeutic Daily Dose

Minimum therapeutic dose that gives a 1/1000th pharmacological effect

$$MACO = \frac{TDD \times MBS}{TDD_N \times SF}$$

1/1000th

Health Based

Minimum dose with toxicological NOAEL

$$MACO = \frac{PDE \times MBS}{TDD_N}$$

- Establishment of a cleaning validation strategy which encompasses two crucial criteria:

4. Results

Introduction of health-based Methodology in MACO calculations

Table 1. Support data for MACO determination

Name	MDD (mg/day)	Batch Size (kg)	Oral PDE (mg/day)
P1	250000	60	2
P2	**2000**	**40**	**2800**
P3	30000	50	1,2
P4	**200000**	**20**	**7,6**

Table 2. MACO determination by the PDE approach

	Name	MACO Worst Case PDE (mg)	MACO P2 Next Batch PDE (mg)	MACO P3 Next Batch PDE (mg)	MACO P4 Next Batch PDE (mg)	MACO P1 Next Batch PDE (mg)
Health Based	**P1**	96	40000	3333	200	480
	P2		56000000	4666667	280000	672000
	P3		24000	2000	120	288
	P4		152000	12667	760	1824

Table 3.MACO determination by the TDD approach

	Name	MACO Worst Case TDD (mg)	MACO P2 Next Batch TDD(mg)	MACO P3 Next Batch TDD (mg)	MACO P4 Next Batch TDD(mg)	MACO P1 Next Batch TDD (mg)
Therapeutic Daily Dose	**P1**	160	5000000	416667	25000	60000
	P2		40000	3333	200	480
	P3		600000	50000	3000	7200
	P4		4000000	333333	20000	48000

MACO was determined by the PDE and TDD criteria assuming both product grouping and the worst-case approach, as evidenced in **tables 2** and **3**. The comparison of the obtained MACO evidenced that the **lowest MACO** derived from the implementation of the health based methodology.

Introduction of a hormone-based product into the shared facility

PRODUCT SEGREGATION NECESSARY?

Table 4. Support data for MACO determination

Name	MDD (mg/day)	Batch Size (kg)	Oral PDE (mg/day)
P1	250000	60	2
P2	**2000**	**40**	**2800**
P3	30000	50	1,2
P4	**200000**	**20**	**7,6**
P5	**800**	**50**	**2,66**

Table 5. MACO determination by the PDE approach

	Name	MACO Worst Case PDE (mg)	MACO P2 Next Batch PDE (mg)	MACO P3 Next Batch PDE (mg)	MACO P4 Next Batch PDE (mg)	MACO P5 Next Batch PDE (mg)	MACO P1 Next Batch PDE (mg)
Health Based	**P1**	96	40000	3333	200	125000	480
	P2		56000000	4666667	280000	175000000	672000
	P3		24000	2000	120	75000	288
	P4		152000	12667	760	475000	1824
	P5		53200	4433	266	166250	638,4

Table 6.MACO determination by the TDD approach

	Name	MACO Worst Case TDD (mg)	MACO P2 Next Batch TDD(mg)	MACO P3 Next Batch TDD (mg)	MACO P4 Next Batch TDD(mg)	MACO P5 Next Batch TDD(mg)	MACO P1 Next Batch TDD (mg)
Therapeutic Daily Dose	**P1**	64	5000000	416667	25000	15625000	60000
	P2		40000	3333	200	125000	480
	P3		600000	50000	3000	1875000	7200
	P4		4000000	333333	20000	12500000	48000
	P5		16000	1333	80	50000	192

The comparison of the obtained MACO, following the introduction of a hormone-based product in the shared facility, evidenced that the **lowest MACO** derived from the implementation of the Therapeutic Daily Dose criteria in detriment of the health based approach. Additionally, the establishement of a well-founded strategy of health based exposure limit (HBEL) determination supported the manufacture of a hormone-based product in shared facilities.

5. Conclusions

The implementation of the PDE criteria, which accounts with a real pharmacological and toxicological evaluation of the medicinal product, impacted the MACO acceptance limit previously implemented in a multipurpose facility. Additionally, the introduction of a hormone-based product into the shared facility did not evidence the need to product segregation, given the implementation of a well-founded health based exposure limit determination, which supported the dispensability of dedicated facilities. Thereby, a revision of the entire cleaning validation process to include this regulatory change and the newly defined cleaning validation strategy evidences to be crucial to ensure compliance with the current regulation.

6. References

[1] European Medicines Agency (EMA). Guideline on setting health based exposure limits in use for risk identification in the manufacture of diferente medicinal products in shared facilities. Nov 2014.

[2] European Medicines Agency (EMA). Questions and answers on implementation of risk based prevention of cross contamination in production and "Guideline on setting health based exposure limits for use in identification in the manufacture of diferente medicinal products in shared facilities". Dec 2016.