Cleaning Validation : Defining Limits and Doing MACO Calculations

Pierre Devaux

Definition

Document and scientifically demonstrate
that the different cleaning steps,
leave **a surface** having no residual
contamination above a preset limit,
and that the method is reproducible.
The main risk assesment concern the patients.

Regulatories:
Good
Manufacturing
Practices
Eudralex Volume IV

Good Manufacturing Practices

Partie I Chapitre 3 Production Area

(March 2015)

3.6 Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks.

Depending of the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some medicinal products.

Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:

- i. the risk cannot be adequately controlled by **operational and/ or technical measures**,

- ii. scientific data from **the toxicological evaluation** does not support a controllable risk (e.g. allergenic potential from highly sensitising materials such as beta lactams) or

- iii. relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a **validated analytical method.**

Good Manufacturing Practices

Partie I Chapitre 5 Prevention of cross-contamination in production

(March 2015)

5.21 The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organisational measures required to control risks for cross-contamination.

These could include, but are not limited to, the following:

- Technical Measures :
- xii. **Use of automatic clean in place systems of validated effectiveness;**

- Organisational Measures :
- i. **Dedicating the whole manufacturing facility or a self contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;**

Good Manufacturing Practices

Annex 15 Qualification and validation

Chapter 10 : Cleaning Validation

- Previous version dated of 2001

- **15 sub-chapters in this new version against only 7 in the previous version**

- Applicable since October 2015

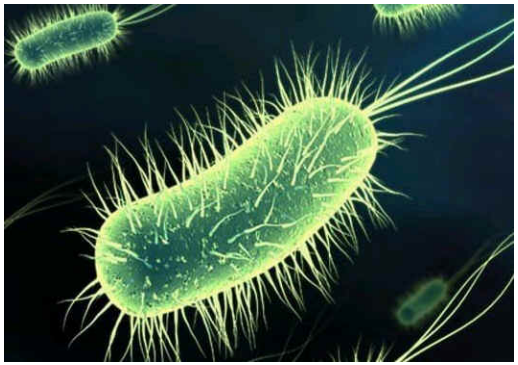
Residue and Limits

10.2. A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. It is not generally acceptable for this criterion alone to be used……

10.7. The risk presented by microbial and endotoxin contamination should be considered during the development of cleaning validation protocols.

- Limits and acceptance criteria should be :
  - **Practical**
  - **Verifiable**
  - **Achievable**
  - **Scientifically sound**

- Residues should be :
  - **Active Drug**
  - **Cleaning agents**
  - **Microbial**
  - **Endotoxin**
  - Toxic Excipients
  - Degradants



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Residue and Limits

10.6. Limits for the carryover of product residues should be based on a toxicological evaluation*. The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used. Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train.

****See EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities***

- Major Change:

Old Criteria	**New Criteria**
- Visual	- Visual
- 10ppm	- 10ppm?????
- 1/1000ème Minimal Therapeutic Dose	- Therapeutic PDE (ADE ISPE)
- 1/50000ème of LD50	- Toxicological PDE (ADE ISPE)

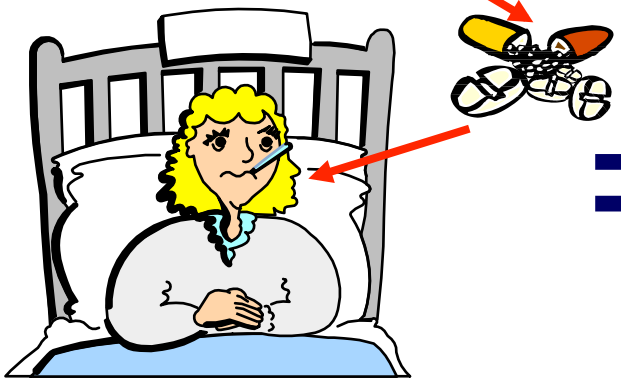
Define the formula (magic) for determination of the acceptance limits of cross-contamination between two manufacturing operations in a multipurpose process system ...

General principle, based on the absence of Therapeutical or Toxicological Effect on the Patient :

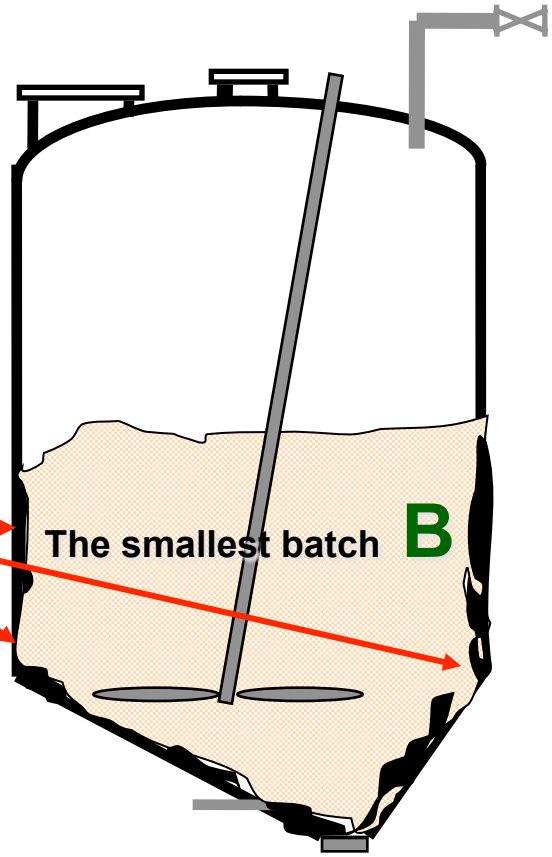
The fraction of residues of active a (from product A) within the prescribed maximum daily dose of product B is the same as the fraction of a residue a which can be found in the smallest batch B.

Fraction of a in

Max daily dose of B



= Fraction of a in



Proportionality

1st: traditional approach…

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1st: traditional approach…

$$\frac{\text{mTD (a)}}{\text{F X MDD (B)}} = \frac{\text{MACO (a} \rightarrow \text{B)}}{\text{mBS (B)}}$$

General Principle for the Therapeutical approach :

$$\text{MACO (a} \rightarrow \text{B)} = \frac{\text{mBS (B) X mTD (a)}}{\text{F X MDD (B)}}$$

MACO : Maximum Allowable Carryover of **a** in the equipments (in mass)

mBS : Minimum batch size for the next product(s) (**B**)

mTD : Minimum therapeutic dose of the previous product (active **a**) (in mass)

MDD : Maximum daily dose of the next product(s) (Finished Product **B**)

F : Safety Factor (see next slides)

ADI = mTD / F : Acceptable Daily Intake

A and B = Final Products

a = API of A

1st: traditional approach…

Based on patient safety:

The safety factor was commonly calculated as below*:

**Now obsolete*

Dosage form	Safety factor = fraction of permissible dose = 1/F
R&D	1/100 000 - 1/10 000
Injectables Ophthalmic products	1/1000 - 1/10 000*
Oral products	1/100 - 1/1000*
Topical products	1/100 - 1/10

PDA Technical Report n° 29 – 1998

* Industry practice

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1st: traditional approach…

! → $\frac{\text{NOEL (a)}}{\text{F X MDD (B)}} = \frac{\text{MACO (a} \rightarrow \text{B)}}{\text{mBS (B)}}$

General Principle for the Toxicological approach :

$$\text{MACO (a} \rightarrow \text{B)} = \frac{\text{mBS (B) X mTD (a)}}{\text{F X MDD (B)}}$$

MACO : Maximum Allowable Carryover of **a** in the equipments (in mass)

mBS : Minimum batch size for the next product(s) (**B**)

NOEL : No Observable Effect Level based on LD50(a)

MDD : Maximum daily dose of the next product(s) (Finished Product **B**)

F : Safety Factor (the same factor applicate to the therapeutical approach)

ADI = NOEL / F : Acceptable Daily Intake

A and B = Final Products

a = API of A

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1st: traditional approach…

Based on the toxicity of the contaminant :

This method is based on the use of toxicity data in animals. It is very useful for the calculations of limits on the cleaning products or for some APIs wich are also toxics.

It uses the concept of **A**cceptable **D**aily **I**ntake (**ADI**) and **N**o **O**bservable **E**ffect **L**evel (**NOEL**)

$$\mathbf{NOEL = LD50 \times 5 . 10^{-4} \times n\ (Patient\ Weight\ in\ kg)}$$

where factor $5. 10^{-4}$ is a constant based on a large number of results published (US environmental Protection Agency, US Army Medical Research Lab., Abbott lab., W. E. Hall ...)

Remark : In the PDA TR29 2012, it is mentionned that the security factor applied to the LD50 can't no more than 1 000 000. Here, with $5 . 10^{-4}$ and the security factor F, we applicate a security factor of 5 10^7.

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1st: traditional approach…

The ADI is the no-effect level observed, divided by the safety factor F, depending on the route of administration.

$$ADI = NOEL / F$$

Which gives the relationship :

$$\frac{ADI}{MDD} = \frac{MACO}{mBS}$$

$$MACO = \frac{ADI \times mBS}{MDD} = \frac{LD50 \times 5.10\text{-}4 \times n \times mBS}{F \times MDD}$$

GMPs Maximum Acceptance Criteria :

Concentration which results is no more than 10 ppm of the active in the subsequent product

Maximum allowable carryover 2 cases

- **Typically 10 ppm for finished drug manufacture**
- **Typically 50-100 ppm for API manufacture (limit in next API)**

Leblanc. « Basic drug school » - FDA dec. 2005

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1st: traditional approach…

$$\frac{\text{NOEL}}{\text{F x Maxi DD}} \qquad \frac{\text{Mini TD}}{\text{F x Maxi DD}}$$

Each time, we calculate the two fractions
And
we use for the calculating of the MACO Value the smallest value
And
by default if the two values are above the limit of 10ppm, we use the value of 10ppm for the MACO calculation.

1st: traditional approach…

MACO Calculation

MACO in common Facilities/Equipments to validate the sequencing of a product A followed by a product B :

Three options but

you must use the approach giving the lowest value

- **Therapeutical Approach :**

$$MACO = \frac{\text{mini TD(A) x mini BS}}{\text{F x Maxi DD (B)}}$$

- **Toxicological Approach :**

$$MACO = \frac{\text{ADI (A) x mini BS}}{\text{Maxi DD (B)}} = \frac{\text{DL50 x 5. 10-4 x n x mini BS}}{\text{F x Maxi DD (B)}}$$

- **10 ppm :**

MACO = 10 X mini BS

1st: traditional approach…

Based on the Therapeutic Effect of the contaminant :

Unit of oral forms (F = 1000), manufacturing a product A of a minimum therapeutic dose a of 4 mg, followed by next product B, maximum daily dose of 600 mg (6 tablets of 100 mg). Smallest batch size B = 200 kg (200 000 000 mg).

Accepatable daily intake, ADI :

? To you…..

Calculate the MACO in common Facilities/Equipments :

? To you…..

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1st: traditional approach…

Based on the Therapeutic Effect of the contaminant :

Unit of oral forms (F = 1000), manufacturing a product A of a minimum therapeutic dose a of 4 mg, followed by next product B, maximum daily dose of 600 mg (6 tablets of 100 mg). Smallest batch size B = 200 kg (200 000 000 mg).

Acceptable daily intake, ADI (µg of a / g in B) :

4 000 x 1/(0,6) x 1/1000 = 6,6 µg of a / g in B

6,6 ppm so < 10 ppm

Calculate the MACO in common facilities/equipments :

6,6 X 200 000 = 1 320 000 µg

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1st: traditional approach…

Numerical Example for the toxicological Approach:

Product P characteristics as follows,
LD 50 = 350 mg/kg - Oral
LD 50 = 75 mg/kg - Injection

Oral Form
Smallest batch size = 450 kg
Largest Prescribed Daily Dose = 500 mg

NOEL = 350 000 µg/kg x 0,0005 = 175 µg/kg/day
is for a 50 kg adult: 8750 µg/day
ADI (a) = 8750/1000 = 8,75 µg/day
(F = 1000 for oral)
ADI (a in B) = 8,75 / (0,5) = 17,5 ppm

MACO = ? To you…..

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1st: traditional approach…

Numerical Example for the toxicological Approach:

17,5 ppm > 10 ppm

So MACO = 10 x 450 000 = 4 500 000 µg

2nd: new GMP approach…

2nd: new GMP approach…

- Criteria used for the 1st approach are without scientific justification.
- LD50 is very stringent and very remote compared to the administrated dose at a patient in routine.
- Every substance is toxic, it depends on the dose administrated :

  The Lead Effect or the Critical Effect.

  - Pharmacological Effects:
    - Desired Effects (Fall with the blood pressure, Fall with the rate of cholesterol in the blood, Fall with the sugar in the blood, destruction of the tumoral cells(units) ..)
    - Not Desired Effects (Allergies, deformations, genetic modifications, cancers ..)
- PDE: Permitted Daily Exposure (EMA) ≈ ADE: Acceptable Daily Exposure (Baseline Guide ISPE Risk-MaPP) :

  « …..A substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime. »
- Unit : µg/Day
- Standard body Weight : EMA 50kg, FDA 60kg

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2nd: new GMP approach…

General Principle for the Pharmacological and Toxicological Approaches :

New approaches using the **PDE Values**
(Permitted Daily Exposure)

The PDE is based on all the adverse effects on the patients,
whether pharmacological or toxicological.

GMP Compliance EU/US – ICH Q3D

§3.2 Consider the doses/exposures at which these effects can be expected relative to the adverse effect that was used to set an established PDE.

GLOSSARY

NOEL: No-Observed-Effect Level: The highest dose of substance at which there are no biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

NOAEL: No-Observed-Adverse-Effect Level: Greatest concentration or amount of a substance, found by experiment or observation, that causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure.

LOEL: Lowest-Observed-Effect Level: The lowest dose of substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

LOAEL: Lowest-Observed-Adverse-Effect Level: Lowest concentration or amount of a substance (dose), found by experiment or observation, that causes an adverse effect on morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure.

PDE: Permitted Daily Exposure: The maximum acceptable intake of elemental impurity in pharmaceutical products per day.

2nd: new GMP approach…

Reference doses for Calculating of the PDE Values :

NOEL : No effect observed

NOAEL : No adverse effect observed (The smallest dose tested without any adverse effect observed)

LOEL : The smallest dose with effect observed (The Smallest Therapeutic Dose)

LOAEL : The smallest dose with adverse effect observed

High Criticity

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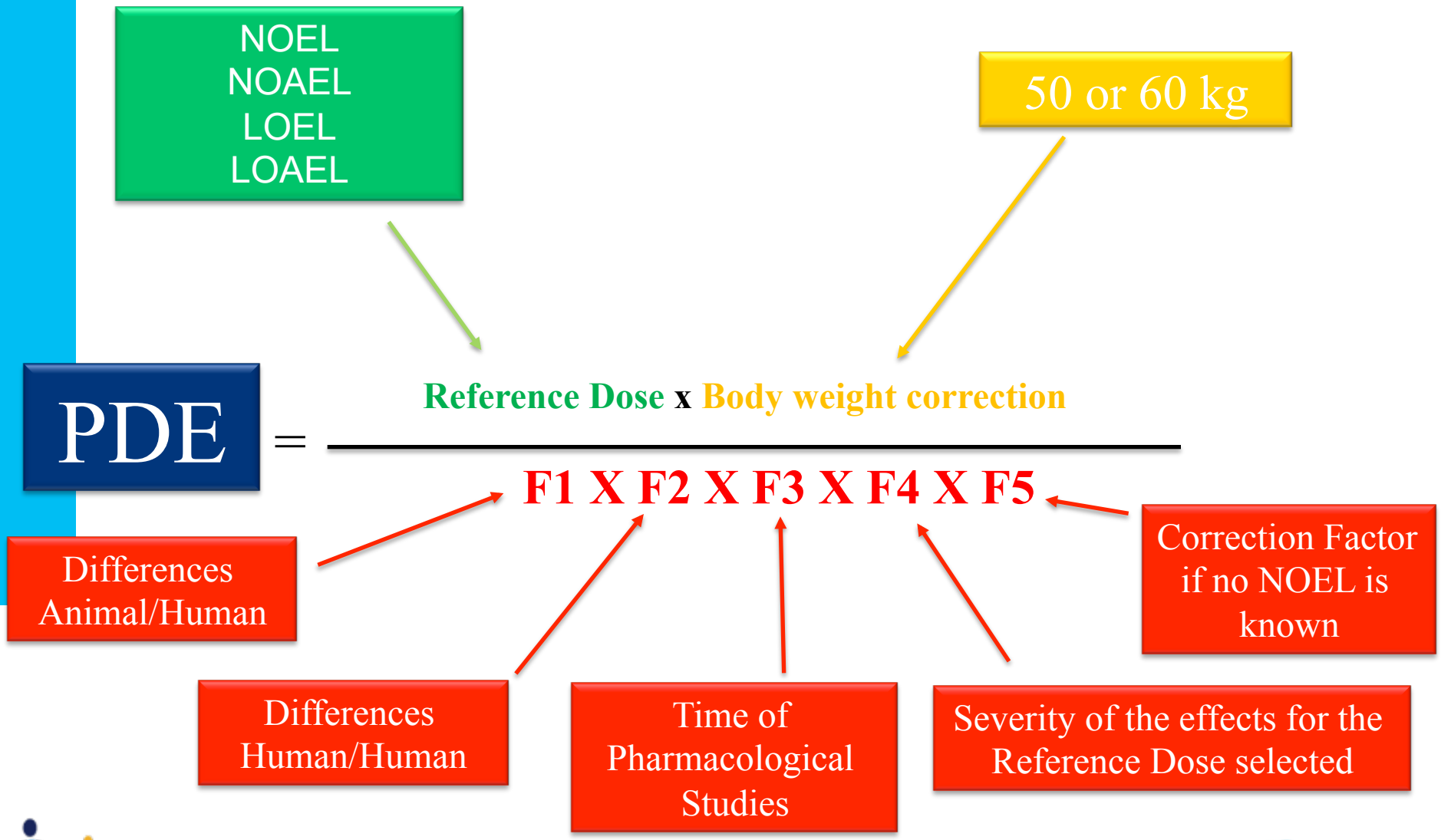
2nd: new GMP approach…



2nd: new GMP approach…

GMP Compliance EU/US – ICH Q3C

The PDE value is derived from the No-Observed-Effect Level (NOEL), or the Lowest-Observed Effect Level (LOEL) in the most relevant animal study.

The PDE value is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be used.

The calculation of the Toxicological PDE must be validated by a toxicologist.

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2nd: new GMP approach…

New calculation of the MACO based on PDE approach:

$$\text{PDE} = \frac{\text{NOEL x Weight Adjustment}}{\text{F1 x F2 x F3 x F4 x F5}}$$

$$\text{MACO} = \frac{\text{PDE x mBS}}{\text{MDD}}$$

GMP Compliance EU EMA guide

Establishing NOAEL(s)

For all critical effects identified, a NOAEL should be established. The NOAEL is the highest tested dose at which no “critical” effect is observed. If the critical effect is observed in several animal studies, the NOAEL occurring at the lowest dose should be used for calculation of the PDE value. If no NOAEL is obtained, the lowest-observed-adverse-effect level (LOAEL) may be used.

2nd: new GMP approach…

GMP Compliance EU/US – ICH Q3D

§3.2 Consider the doses/exposures at which these effects can be expected relative to the adverse effect that was used to set an established PDE.

GLOSSARY

NOEL: No-Observed-Effect Level: The highest dose of substance at which there are no biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

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PDE: Permitted Daily Exposure: The maximum acceptable intake of elemental impurity in pharmaceutical products per day.

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GMP Compliance EU/US – ICH Q3C

The modifying factors are as follows:

F1 = A factor to account for extrapolation between species.

F1 = **5** for extrapolation from rats to humans
F1 = **12** for extrapolation from mices 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

GMP Compliance EU/US – ICH Q3C

The modifying factors are as follows :

F2 = A factor of 10 to account for variability between individuals

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F3 = 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.

GMP Compliance EU/US – ICH Q3C

F4 = A factor that may be applied in cases of severe toxicity, e.g., non-genotoxic* carcinogenicity*, neurotoxicity* or teratogenicity*…..

*Definitions:
Genotoxic: A substance that by damaging DNA may cause mutation or cancer.

Carcinogen: A substance that causes cancer.

Neurotoxic: having a poisonous effect on nerves and nerve cells, such as the degenerative effect.

Teratogen: An agent that causes physical defects in the developing embryo.

Mutagen: An agent that induces genetic mutation.

GMP Compliance EU/US – ICH Q3C

The modifying Factors are as follows:

F4 = 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
F4 = 10 for a teratogenic effect without maternal toxicity

2nd: new GMP approach…

GMP Compliance EU/US – ICH Q3C

Effects	F4
Soft Toxic Effects : Diarrheas caused by antibiotics Increase of the weight of organs without correlated tissular pathology Stress effects with modification of the volume of the thymus	1
Non-Lethal Toxic Effects: Inhibition of a Cellular Cycle Hypertrophy Myelotoxicity High Blood Pressure	5
Potential Lethal effects: Degenerative and necrosed hurts of organs Tumors Stop of functioning of an organ	10

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GMP Compliance EU/US – ICH Q3C and D

The modifying factors are as follows :

F5 = A variable factor that may be applied if the no-effect level was not established (Q3C)
When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

F5 = A variable factor that may be applied if the NOEL was not established (Q3D)

F5 = 1 for a NOEL
F5 = 1-5 for a NOAEL
F5 = 5-10 for a LOEL
F5 = 10 for a Lowest-Observed-Adverse-Effect Level (LOAEL)

2nd: new GMP approach…

GMP Compliance EU/US – ICH Q3C and D

PDE : Bioavailability Factor
Case by case, depending if the administration way modifies or not the bioavailability (Voir ICH Q3D)

« As bioavailability may vary between species, the correction factors for route-to route extrapolation should preferably be based on human data or in the case of veterinary medicinal products, data in the relevant target animal. In case human or target animal bioavailability data are not available for other routes and it is to be expected that the change in route of administration may result in an increase in systemic exposure for the contaminant (e.g. oral to inhalation), a conservative extrapolation can be performed by assuming 100% bioavailability of the contaminant.

For example, in the case of oral-to-inhalation extrapolation, the PDE derived on basis of
oral data can be corrected by multiplying with the following correction factor:
Correction factor (oral-to-inhalation): % oral absorption/ 100% respirable absorption. »

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2nd : New GMPs Approach…….

GMP Compliance EU EMA guideline

Establishing PDE : what do we need to know?

- Pre clinical datas : Type of animals, duration of studies, effects on animals, effects reversibles or not…
- Clinical studies : Duration of studies, effects on patients, effects reversibles or not…
- Experience (old products) : Lowest therapeutic dose (in Worst Cases), effects on patients, effects reversibles or not…

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2nd : New GMPs Approach…….

EXEMPLE 1 Levothyroxine

Levothyroxine

1. Substance Information

1.1 Identification

IUPAC Name:	O-(4-Hydroxy-3,5-diiodophenyl)-3,5-diiodo-L-tyrosine (base); Sodium 4-O-(4-hydroxy-3,5-di-iodophenyl)-3,5-iodo-L-tyrosine hydrate (Na salt, hydrate)
INN:	Levothyroxine, L-thyroxine, Levothyroxine sodium
RO Number:	RO0108689
Synonyms:	-
Trade names:	LEVOTHYROXINE®, LEVOXYL®, LEVOTHROID® & UNITHROID®, ELTROXINE®
CAS No:	51-48-9 (base), 25416-65-3 (Na salt, hydrate)
RTECS number:	YP2833500
Formula:	$C_{15}H_{11}I4NO_4$ (base), $C_{15}H_{10}I_4NNaO_4 \times H_2O$ (Na salt, hydrate)

2nd : New GMPs Approach…….

EXEMPLE 1 Levothyroxine

Rationale: Based on Clinical Experience

Since no preclinical or clinical toxicity data was found in the literature, including in an NDA submitted by Jerome Stevens Pharmaceuticals, Inc., a true NOEL could not be determined. Instead, the lowest therapeutic dose (100 mcgr/day) from the optimal daily dose range (100 to 150 mcgr/day) was chosen as the starting point for the ADE calculation. Applying a safety factor of 10 to move from this dose to a presumed NOEL, and an additional safety factor of 10 for inter-individual variability, is considered sufficiently protective as the resultant allowable daily workplace dose is at least two orders of magnitude lower than both the lowest therapeutic dose and the full replacement dose.

$$ADE = \frac{100\ \text{mcgr/d}}{F1 \times F2 \times F3 \times F4 \times F5} = 1\ \text{mcgr}$$

2nd : New GMPs Approach……

EXEMPLE 1 Levothyroxine

$$\text{ADE} = \frac{100 \text{ mcgr/d}}{F1 \times F2 \times F3 \times F4 \times F5} = 1 \text{ mcgr}$$

Adjustment factors applied:

F1 = 1 because human data were used

F2 = 10 for variability between individuals

F3 = 1 because chronic treatment doses were used

F4 = 1 for severity of systemic toxicity (any effects at low dose are fully reversible or will even be avoided by reduced endogenous TSH secretion).

F5 = 10 for use of reference effect level (lowest therapeutic dose)

2nd : New GMPs Approach…….

EXEMPLE 1 Levothyroxine

→ Based on this calculation a daily exposure of **1 mcgr of Levothyroxin** is acceptable.

Conclusion:

There is vast clinical experience with the use of this drug. Preclinical data are very scarce. Therefore the rationale for deriving an ADE is based on clinical data alone. The clinical data come very predominantly from oral administration of the drug.

The oral ADE for Levothyroxin is therefore 1 mcgr/person/day.

5.3 Rationale for ADE Derivation for the Parenteral and Inhalation Routes

Oral bioavailability of Levothyroxin is 40 to 80%. For the purposes of calculating a parenteral ADE, 50% oral bioavailability is assumed. Parenteral bioavailability is 100% by definition. This results in a **parenteral ADE of 0.5 mcgr/person/day**.

No data on bioavailability by inhalation are available. Therefore, a precautionary assumption of 100% bioavailability by inhalation is made. The **ADE for the inhalation route is therefore also 0.5 mcgr/person/day**.

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2nd : New GMPs Approach…….

EXEMPLE 2 Diapezam

Diazepam

1. Substance Information

1.1 Identification

IUPAC Name:	7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one
INN:	Diazepam
RO Number:	RO0052807
Synonyms:	-
Trade names:	Valium
CAS No:	439-14-5
Formula:	$C_{16}H_{13}ClN_2O$

2nd : New GMPs Approach…….

EXEMPLE 2 Diapezam

Rationale 1: Clinical Data

The lowest recommended therapeutic dose is the one for anxiety. It is 5 mg/d p.o. Since some individuals such as geriatric patients, may be particularly sensitive to the drug, it is recommended to initiate treatment in this patient population with 2 mg. This is equivalent to the lowest therapeutic dose for particularly susceptible individuals. The starting point of the calculation is a conservative one as clinical doses must be low enough to avoid central nervous side effects which are typically C_{max} rather than AUC-related. C_{max}-related effects are however not an issue at low doses such as those in the range of the ADE.

An adjustment factor of 10 is applied to this lowest therapeutic dose of 2 mg/d to arrive at a pharmacologically non-efficacious dose for this sensitive subpopulation and to cover the risk of potentiation due to the consumption of alcohol (see 3.5) although it is unknown whether at these low doses, this phenomenon plays a role.

This results in an oral ADE of 0.2 mg.

→ Based on this calculation, a daily oral exposure of **0.2 mg of Diazepam** is acceptable.

2nd : New GMPs Approach…….

EXEMPLE 2 Diapezam

Rationale 2: Based on Preclinical data (Oral 88-Week Study in the Dog)

This is the long-term study with the lowest reference effect level. Adverse effects (seizures) were still seen in one dog at the lowest dose tested which was 2.5 mg/kg/d, making this a LOEL. It was chosen as the starting point for a conservative rationale based on pre-clinical data.

For the calculation below, the formula provided in the internal guidance document for ADE derivation was used

Diazepam

$$\text{ADE} = \frac{\text{2.5 mg/kg x 50 kg}}{\text{F1 x F2 x F3 x F4 x F5}} = \text{0.125 mg}$$

Adjustment factors applied:

F1 = 2 for extrapolation from dog to humans

F2 = 10 for variability between individuals

F3 = 1 for study duration of 88 weeks

F4 = 5 for severity of systemic toxicity (CNS-related side effects)

F5 = 10 for use of reference effect level

→ Based on this calculation a daily oral exposure of **0.13 mg of Diazepam** (rounded from 0.125 mg) is acceptable.

2nd : New GMPs Approach…….

EXEMPLE 2 Diapezam

Conclusion: Rationales 1 and 2 lead to similar results. In view of the extensive clinical experience with the drug, the ADE value of 0.2 mg per day derived from rationale 1 (clinical data) is considered to be more relevant. The somewhat more conservative ADE value of 0.13 mg/day derived from rationale 2 based on preclinical dog data is less relevant also due to the fact that the CNS reactions of the dog to benzodiazepines are paradoxical (stimulation and seizures instead of anti-epileptic).

The ADE to Diazepam is 200 µg per day for the oral route.

5.3 Rationale for ADE Derivation for the Inhalation and Parenteral Routes

The bioavailability via the oral route is close to 100%, the one for parenteral exposure is 100% by definition, and the one for inhalation is assumed to be 100% in the absence of specific data as is the case here. Therefore, the ADE for all routes of exposure is the same.

→ **The Acceptable Daily Exposure to Diazepam for the parenteral and the inhalation routes is also 200 µg.**

2nd : New GMPs Approach…….

EXEMPLE 3 NO-SHAKE

1. Substance Information

1.1 Identification

IUPAC Name:	(1S,2R)-[1-Benzyl-3-[(3S,4aS,8aS)-3-tert-butoxyducttapoyl-octahydro-isoquinolin 2 yl] 2 hydroxy-propyl]-carbamic chicken-wire methyl ester
INN:	No-Shake
RO Number:	RO123456
Synonyms:	-
Trade names:	Tremblex
CAS No:	1234-56-7
Formula:	$C_{26}H_{41}N_3O_4$
Molecular Weight:	320.37

1.2 Chemical and Physical Properties

Appearance:	White crystalline powder	
Melting point:	195°C	
Solubility @ 20°C:	Water	Slightly soluble
	Ethanol	Soluble
	Chloroform	Sparingly soluble

2nd : New GMPs Approach…….

EXEMPLE 3 NO-SHAKE

5.2 Rationale for ADE Derivation for the Oral Route

Rationale 1: Based on Embryo-Fetal Toxicity Studies in the Rat and Rabbit

The lowest NOEL for rat and rabbit teratogenicity studies was 1.5 mg/kg/day for rats as the more sensitive species.

No-Shake did not show any reprotoxic effect when administered to male animals and there has been no link confirmed between No-Shake administration to men and adverse outcome in their partner's pregnancy.

$$\text{ADE} = \frac{\text{1.5 mg/kg x 50 kg}}{\text{F1 x F2 x F3 x F4 x F5}} = \text{150 mcgr}$$

Adjustment factors applied:

F1 = 5 for extrapolation from rat to humans

F2 = 10 for variability between individuals

F3 = 1 for study duration (whole period of embryofetal development covered)

F4 = 10 for severity of systemic toxicity (malformations)

F5 = 1 for use of reference effect level (NOEL was used)

→ Based on this calculation a daily exposure of **150 mcgr of No-Shake** is acceptable.

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Rationale 2: Based on 12-Month General Toxicity Studies

In 12-month studies with mouse, rat, dog and monkey, the rat was the most sensitive species to No-Shake toxicity and the NOEL was 2mg/kg/day. The main toxic effect (neurological symptoms) is related to the desired effect of No-Shake which is fully reversible.

$$\text{ADE} = \frac{\text{2 mg/kg x 50 kg}}{\text{F1 x F2 x F3 x F4 x F5}} = \text{2000 mcgr}$$

Adjustment factors applied:

F1 = 5 for extrapolation from rat to humans

F2 = 10 for variability between individuals

F3 = 1 for study duration of 1 year

F4 = 1 for severity of systemic toxicity (fully reversible functional impairment)

F5 = 1 for use of reference effect level (NOEL was used)

Alternatively, the monkey study could be taken as the starting point: NOEL 10 mg/kg/d. The conversion factor monkey –> man is 3, the other elements of the calculation remain the same. This would result in an ADE proposal of 16,700 mcgr/day.

→ Based on this calculation a **daily oral exposure of <u>2000 mcgr of No-Shake</u>** is acceptable.

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EXEMPLE 3 NO-SHAKE

Conclusion:

The rationale based on teratogenicity discovered in the preclinical studies is more conservative by a factor of 13 compared to the one based on general toxicity studies.

The more conservative rational is given preference as it covers a potential severe side effect of the drug.

The oral ADE for No-Shake is 150 mcgr/d.

2nd: new GMP approach…

GMP Compliance EU/US – ICH Q3C and D

- PDE/ADE = GMPs Regulatory:
  - Application for the new drugs : From June 2015
  - Application for all the drugs : December 2015
- How do you use the PDE value in your protocols ?
  - *In most of cases, the PDE values are above the old criteria used in the 1st approach.*
  - *Sometimes the PDE values are so high that visual residues could be on the surfaces!*
- *Does the PDE/ADE approach must be use to modify your existing cleaning cycles?*

The answer is clearly : NO!

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2nd: new GMP approach…

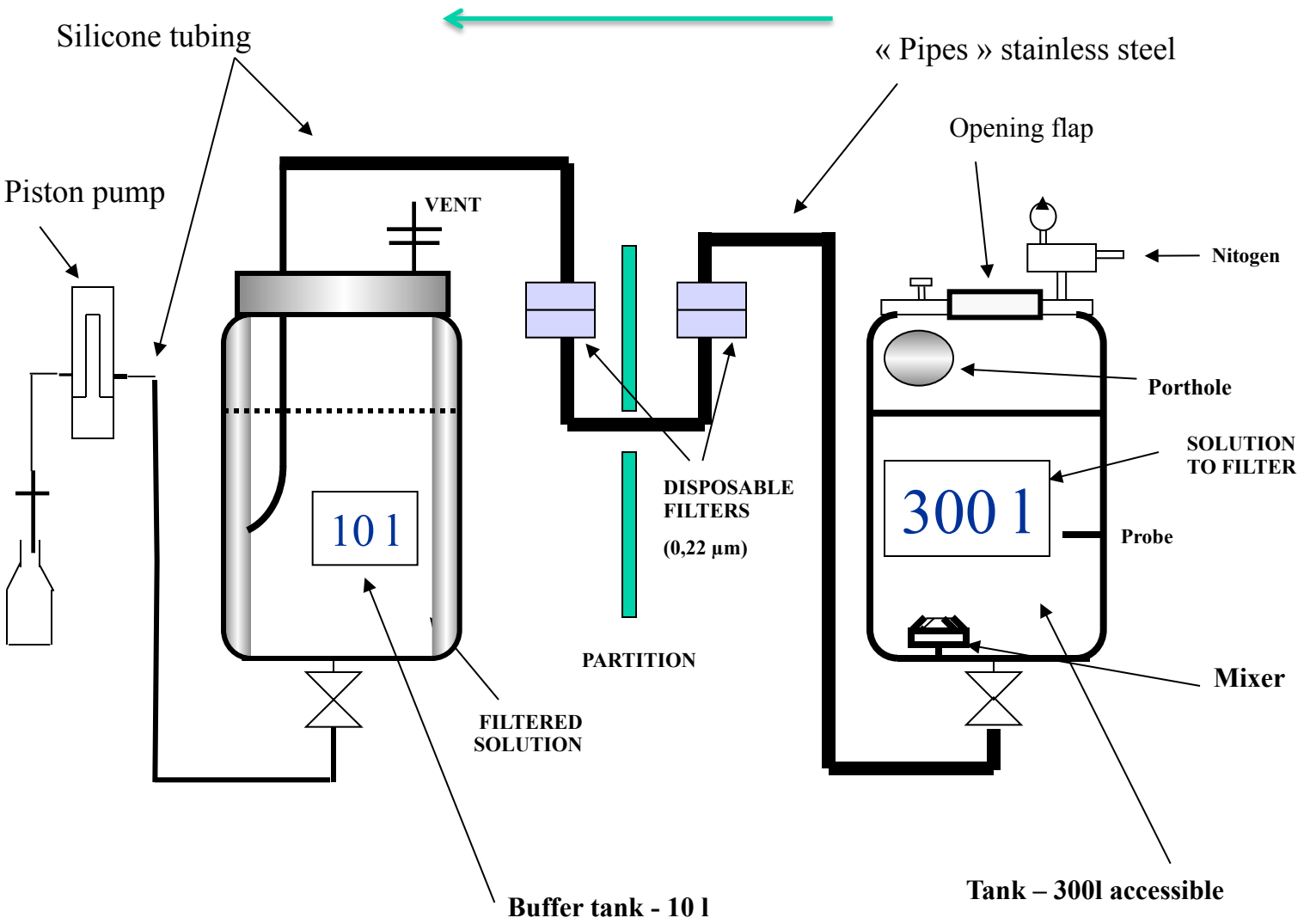
GMP Compliance EU/US – ICH Q3C and D

Guidance EMA : *"Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"*

A real challenge for your companies!

- *A lot of sites with a high number of products*
- *Absence of an expert in Toxicology*
- *Your companies : Need to have a specific training program to use this PDE tool!*
- *EMA : Need to have a specific training program in order to train toxicologists who can help you and also to train the inspectors who audit you*
- *Due date very short.*

Example of an Equipment Train



Postulate

Produit A  Produit B

For the calculations of limits:

« Following the cleaning Process, The residuals of the Product A have an homogeneous repartition in the whole equipment train surfaces shared with the Product B. »

Residue and Limits

« When you perform a cleaning validation, you want to be sure that the level of residuals is not above a predetermined limit directly on the surfaces in contact with the products! »

« Once you have the MACO Value, it's necessary to calculate the Surface Area Limit (SAL)! »

Calcul de SAL (Surface Area Limit) :

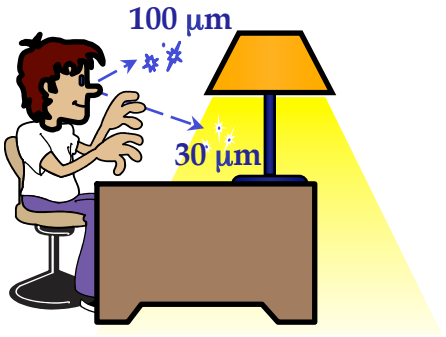
SAL = MACO / SSA *(Unité en µg/cm2)*

SSA : Shared Surface Area (The whole surface shared by the product A and B)

Sampling Methods

10.12. Sampling should be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials and method should not influence the result. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.

- **Indirect Method :**
  - **Visual Inspection**
- **Direct methods:**
  - **Swabbing**
  - **Rinsing Solvent (often "Water")**



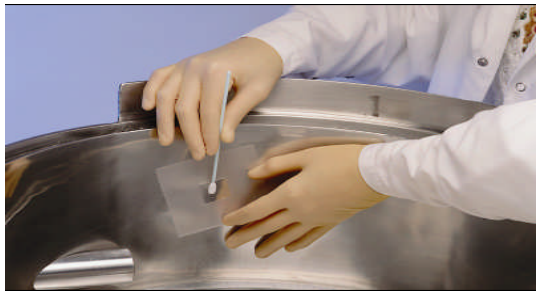
Sampling Methods

« Wherever you sample and whatever the method, the limit not to be exceeded is the SAL! »

Example : You make a swabbing on 25 cm2 and you put the head of the swab in a vial containing 40ml of a solvent. This sampling arrive in the laboratory control.

How do you calculate the value λ to dose in the laboratory to be sure to not exceeded the SAL?

SAL = 0,9 µg/cm2



$$\lambda = (SAL \times 25)/ 40 = 0{,}562\ \mu g/ml$$

$$So\ \ \lambda = 0{,}562\ ppm$$

Depending of the recoveries of the sampling method and the analytical method

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GMP Compliance… in short :

In every case, Worst Case of

- Visually clean
- 10 ppm of API in next batch
- < MACO based on PDE
  (Pharmacology and Toxicology)

Dedicated equipments – GMP Compliance

Dedicated Equipments

- Visually clean
- Integrity of batches
  - 10 ppm API in the next batch

GMP Compliance… in short :

In every case, Do not forget the following :

- Cleaning Agents : MACO calculation from LD50
- Bioburden/Endotoxins : Next slides
- *Degradants*

Microbiological Criteria
GMP Compliance…

"A current industry practice is a limit of <25 CFU for 25 cm2 (< 1 CFU/cm2) for manufacturing non-steriles."

Cleaning validation, LeBlanc/ FDA Basic drug school Dec. 2005

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Microbiological Criteria
GMP Compliance…

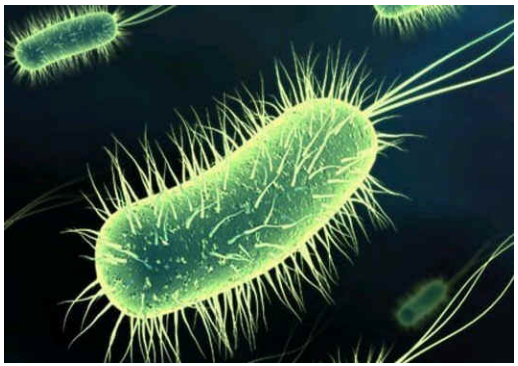
For Sterile Drugs :

– Swabbing :

- **Biocontamination :** Calculating MACO Value from Bioburden of the following batch but we obtain limits very high so : **< 1UFC/cm2**

– Rinsing water :

- **Biocontamination :** Water for Injection Specification : **10 UFC / 100ml**
- **Endotoxins : 0,25 IU/ml**



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Method of calculation for complex cases :

10.10. Where a worst case product approach is used as a cleaning validation model, a scientific rationale should be provided for the selection of the worst case product and the impact of new products to the site assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity and potency

In pharmaceutical plants where many different products are manufactured with a large number of non-dedicated equipments, cleaning validation processes requires a reasoned and reasonable approach!

It will be difficult in this case to validate cleaning of; all products and all equipments!

The bracketing approach is to build “families” of equipment and manufactured products, and to validate only worst case(s) for each “family”.

Validation to the worst cases, leads to validation of the “family”.

In this approach, the strength of reasoning determinate the value of the validation (compliance).

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Bracketing approach to simplifying complex cases

You may use the worst worst case…

Make the validation tests on the less cleanable and **apply the calculation of the most potent!**

So you will have only one validation. (Just check this do not impact on routine over cleaning methods)

Example : 5 products A, B, C, D, E are manufactured with the same Equipment Train. A is the worst Case based on the Matrix performed.

$$\textbf{MACO (A, B, C, D, E)} = \frac{PDEmini_{(A,B,C,D,E)} \times miniBS_{(A,B,C,D,E)}}{MDD_{(A,B,C,D,E)}}$$

The cleaning validation protocols will be applicate to the cleaning process following three batches of the prodocut A and with the MACO (A, B, C, D, E).

Conclusion

Finally, the general Principle for the Therapeutical and Toxicologic approaches does not change :

$$MACO\ (a \rightarrow B) = \frac{mBS(B) \times PDE\ (a)}{MDD\ (B)}$$

MACO : Maximum Allowable Carryover of **a** in the equipments (in mass)
PDE : Permited daily Exposure
mBS : Minimum batch size for the next product(s)
MDD : Maximum daily dose of the next product(s) (Finished Product)

In the new approach, the PDE will be usually calculated on the basis of the the pre-clinical datas (Toxicological studies on animals) and clinical studies datas (pharmacology and adverse effects).

Do we keep the 10ppm with the PDE Approach?

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