Permitted Daily Exposure Determination Strategy for Molecule Name:_____

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1. Basic Information

a. Client name and address:

Company Name:
Company Address:
Assessment Review Date:

b. Active Pharmaceutical Ingredient details

IUPAC Name:
Chemical Abstract Services (CAS) Registry Number:
Chemical Formula:
Molecular Weight:
Chemical Description and Physical Properties:
Structure:
Solubility of Active Ingredient:
Indication for which drug to be used:

c. Route of administration of formulation/ material

Route of administration: Oral solid/ Injectable (specify method)/ Ophthalmic etc.

d. Objective

The objective of this document is to determine Permitted Daily Exposure (PDE) limit of an active pharmaceutical ingredient. The value will help to identify control cross-contamination risk of drug products that are manufactured in the shared production facilities. Pharmacological and toxicological data including clinical and non-clinical are evaluated to determine PDE value.

The PDE value will help to determine health based exposure limits for a residual active substance.

Reference: Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities
20 November 2014
EMA/CHMP/ CVMP/ SWP/169430/2012.

e. Assessor information

Name of assessor:

Date of completion of assessment:

Sign and date:

2. Hazard Identified

Types of studies	Yes	No	Unknown
Pre-clinical Pharmacodynamics data			
Genotoxicity			
Reproductive developmental toxicity			
Carcinogenicity			
Highly Sensitizing potential			
Repeat dose toxicity			
Target organ toxicity			
Other toxicity identified in animal studies			
Acute Toxicity			
Local tolerance studies			

Hazard category:

Impact of Hazards:

Detailed information and basis for the PDE:

i. Pre-clinical Pharmacodynamics data:

ii. Genotoxicity:

iii. Reproductive developmental toxicity:

iv. Carcinogenicity:

v. Highly Sensitizing potential:

vi. Repeat dose toxicity:

vii. Target organ toxicity:

viii. Other toxicity identified in animal studies:

ix. Acute Toxicity:

x. Local tolerance studies

“Lead” Critical effects

3. Determination of adjustment factors

a. F1: A factor (values between 2 and 12) to account for extrapolation between species

Note: Describe basis for selection of value

b. F2: A factor of 10 to account for variability between individuals

Note: Describe basis for selection of value

c. F3: A factor 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4-weeks

Note: Describe basis for selection of value

d. F4: A factor (1-10) that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity

Note: Describe basis for selection of value

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

Note: Describe basis for selection of value

4. Permitted Daily Exposure (PDE) Calculation

Determination of a PDE involves
(i) Hazard identification by reviewing all relevant data
(ii) Identification of “critical effects”
(iii) Determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered to be critical effects
(iv) Use of several adjustment factors to account for various uncertainties

Appendices 3 of the ICH Q3C and VICH GL 18 guidelines present the following equation for the derivation of the PDE:

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

F1: A factor (values between 2 and 12) to account for extrapolation between species
F2: A factor of 10 to account for variability between individuals
F3: A factor 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4-weeks
F4: A factor (1-10) that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity
F5: A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

5. Reference(s)

a. Reference guidelines

For Example:

1. https://www.ema.europa.eu/en/setting-health-based-exposure-limits-use-risk-identification-manufacture-different-medicinal

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

First published: 24/11/2014
Last updated: 24/11/2014
EMA/CHMP/CVMP/SWP/169430/2012

URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-setting-health-based-exposure-limits-use-risk-identification-manufacture-different_en.pdf

3. Guideline on setting of health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. Date of coming into effect in June 2015. European Medicines Agency (EMA/CHMP/CVMP/SWP/169430/2012) http://www.ema.europa.eu

4. ICH guideline Q3C (R6) on impurities: guideline for residual solvents, EMA/CHMP/ICH/82260/2006,
http://www.ema.europa.eu/docs

b. Reference literatures for hazard identification and other toxicological information

For example:

https://pubchem.ncbi.nlm.nih.gov

https://www.drugbank.ca

https://www.whocc.no

https://www.ema.europa.eu/en/documents/assessment-report/.....

https://www.accessdata.fda.gov/

https://www.webmd.com

6. Summary of the Expert Curriculum vitae (CV)

Name of toxicologist:

Name of organization:

Education qualification:

Credentials and professional affiliates:

Experience:

7. Glossary

8. Supporting attachments