Permitted Daily Exposure Determination Strategy

Name of Molecule:_________________

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

<table>
<thead>
<tr>
<th>Types of studies</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
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</thead>
<tbody>
<tr>
<td>Pre-clinical Pharmacodynamics data</td>
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<tr>
<td>Genotoxicity</td>
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<td>Reproductive developmental toxicity</td>
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<tr>
<td>Carcinogenicity</td>
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<td>Highly Sensitizing potential</td>
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<tr>
<td>Repeat dose toxicity</td>
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<td>Target organ toxicity</td>
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<tr>
<td>Other toxicity identified in animal studies</td>
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<tr>
<td>Acute Toxicity</td>
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<tr>
<td>Local tolerance studies</td>
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</table>

**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:

\[
PDE = \frac{\text{NOAEL} \times \text{Weight Adjustment}}{F_1 \times F_2 \times F_3 \times F_4 \times F_5}
\]

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:


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


   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://www.drugbank.ca
https://www.whocc.no
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