CEHTRA

SCIENCE BEYOND
REGULATORY COMPLIANCE

PDE: standard/tailored thorough monographs

QSAR: Impurities safety qualification ICH M7

HSE: OEL/OEB derivation, CLP classification & on-site audits

ERA: Complete Environmental Risk Assessment for MAA

Your compliance dossiers are in safe hands

Toxicology and Ecotoxicology expertise
QSAR experts*
HSE experts
High Quality Regulatory compliance
Comprehensive ERA monographs

Expertise

PDE

QSAR

HSE

ERA

* QSAR's in partnership with KREATiS

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What is HBEL?

PDE

Permitted Daily Exposure

For patients' health

What defines the PDE?:

In Europe Guideline EMA/CHMP/ CVMP/ SWP/169430/2012;
EMA/CHMP/CVMP/SWP/463311/2016 (Q&A);
EMA/CHMP/CVMP/SWP/246844/2018 (Q&A)
Zones ICH: ICH Q3C (R4) - ICH Q3D – ICH M7(R1) - VICH GL 18

Why do a PDE?

For each API in your manufactured Drug Product,
PDE value will help you :

- Calculating MACO (Maximum Allowable Carry Over): the residual quantity of product that can reasonably be transfered to the next production lot
- Demonstrating that your manufacturing cleaning process is appropriate,
- Designing shared or dedicated manufacturing units according to your product safety profile

OEL

Occupational exposure limit

For workers' health

Why do a OEL?

Ensuring the safety of your employees by using the adapted Risk Management Measure after defining a safe threshold of airborne concentration of an API, in mg/m3 (OEL) in your manufacturing environment.

Why do a OEB?

When OEL cannot be precisely defined, the API can be put within a OEB (Occupational Hazard Band)

The same approach to determine a PDE or an OEL

Determine a Point of Departure (PoD) on Maximal animal threshold dose devoid of critical health effect (NOAEL) Minimal animal threshold dose showing a critical effect (LOAEL) Minimal therapeutic dose in humans

PDE: Maximal threshold of API, in mg/day, devoid of health effects upon chronic exposure when included as a residue in the next product :

$$\text{PDE mg/day} = \frac{\text{PoD (mg/kg bw/day) x Weight adjustement}}{\text{(F1) x (F2) x (F3) x (F4) x (F5) x (F6) x (}\alpha\text{)}}$$

Safety Factor : F1: Intespecies extrapolation F2: intraspecies variation F3: long-term exposure extrapolation F4: severe toxicity F5: no-effect threshold extrapolation F6: lack of safety data alpha: API bioavailability

OEL: PDE should be adjusted to a daily occupational exposure: inhalation route should be considered, value expressed in mg/m3

- Peer-reviewed, stand alone **PDE monographs** for your APIs, excipients, solvents, adjuvants, compliant to EMA guideline prerequisites, either adjusted to company's standards or from CEHTRA PDE catalog
- **Priorisation of PDE** documentation attached to your cleaning validation processes, by screening your substances according to their safety concern: extraction of Toxicological Reference Values from scientific and regulatory data bases
- **Derivation of OEL/OEB** applicable to occupational exposure monitoring and management in your facilities.

CEHTRA
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for your product portfolio

France, Belgium, UK, Spain, Germany, Canada, India

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