How can Occupational Toxicology support Quality: OEL and PDE of Pharmaceuticals

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Definitions

Occupational Exposure Limit

• An **OEL** is set at a level at which, based on current scientific knowledge, it is *judged* that there is minimal risk to the health of the workforce if exposed via inhalation to the substance day after day.

Permitted Daily Exposure

• A **PDE** is a dose that is *unlikely* to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime.
Application of PDE

\[ \text{Maximal Daily Dose} \ (2) = \text{Batch size} \ (2) \]

- PDE\(^{(1)}\)
- Safe carry over\(^{(1)}\)

Diagram:
- Centrifugation
- Drying
- Product
Is PDE correlated with OEL?

**PDE**
- Safe level for chronic exposure, 80 years
- Exposure daily
- IV, oral, other routes
- Depends on the potency (activity) of the substance
- Applied for cleaning validation (equipment)
- Target population **patients** (50kg)

**OEL**
- Safe level for chronic exposure, 40 years
- Exposure daily
- Inhalatory route
- Depends on the potency (activity) of the substance
- Applied for OH (personal monitoring)
- Target population **healthy adults** (70kg)
Is PDE correlated with OEL?

- Steps for determining the PDE and OEL are the same

Hazard identification
  - Identify all the data about the drug

Hazard assessment
  - Determine the critical effect
  - Adjust the safe level to the most sensitive population
  - Adjust the differences and route of exposure
  - Calculate the safe level

Risk assessment
How is the calculation done?

- Several approaches of calculations are provided.
- The critical and the most relevant is selected for three different routes of administration.
- AFs are based on guidances, their application depends on:
  - Experts involved
  - Historical differences

### 7 DETERMINATION PERMITTED DAILY EXPOSURE (PDE)/OCCUPATIONAL EXPOSURE LIMIT (OEL)

#### 7.1 Approach 1 for calculation

#### 7.1.1 Determination of the point-of-departure (POD)

<table>
<thead>
<tr>
<th>POD</th>
<th>Value</th>
<th>Critical effect observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOEL from 13 week oral repeated dose study on rats</td>
<td>5 mg/kg/day</td>
<td>No signs of bone marrow hypoplasia and related anaemia and lymphopenia, no centrlobular hepatocyte degeneration.</td>
</tr>
</tbody>
</table>

#### 7.1.2 Determination of adjustment factors (AF)

<table>
<thead>
<tr>
<th>Adjustment factors</th>
<th>Value IV</th>
<th>Value oral</th>
<th>Value inhalation</th>
<th>Rationale for value selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interspecies variability</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>Extrapolation from rat to human</td>
</tr>
<tr>
<td>Intraspecies variability</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>General factor for difference between individuals within an exposed population</td>
</tr>
<tr>
<td>LOAEL to NOAEL</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>PoD is NOEL</td>
</tr>
<tr>
<td>Duration of exposure</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>13 week study in rodents</td>
</tr>
<tr>
<td>Database completeness</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Dataset complete, quality of data sufficient.</td>
</tr>
<tr>
<td>Severity of effect</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>Safety factor for reproduction/development.</td>
</tr>
<tr>
<td>Bioaccumulation</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Not observed</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>1.4</td>
<td>1</td>
<td>1.4</td>
<td>Factor applied for different route of exposure</td>
</tr>
<tr>
<td>Composite Adjustment Factor (CAF)</td>
<td>1030</td>
<td>750</td>
<td>1050</td>
<td>100% systemic bioavailability (IV/inhalation) = 1.4</td>
</tr>
</tbody>
</table>

Bioavailability = \[
\frac{100\% \text{ systemic bioavailability (IV/inhalation)}}{72\% \text{ systemic bioavailability (oral)}} = 1.4
\]
What are the consequences for workers

• OELs in Novartis are being updated since 2014

• Risk assessments need to be conducted in case a change is significant
Harmonization of the hazard assessment

- Comparison of EPA and WHO values
- 65 chemicals
- Slightly different time, method, data
- 30% were identical
- 60% of values were within 3-fold difference
- 9% of values within 300-fold difference
- 1 chemical 700-fold difference
- EPA values lower than WHO
What does this mean?

• Changes up to 3-fold are “trivial” and are generally not significant for risk assessment
  – 0.5 ug/m3 and 1.5 ug/m3 is virtually the same
  – 5 ug/m3 and 15 ug/m3 is virtually the same
  – 50 ug/m3 and 150 ug/m3 is virtually the same

• Proper communication is essential to assure people their health is not in jeopardy
  – Especially important for industrial hygienists and occupational medical personnel that are in contact directly with the workers

• Challenge with banding approaches
Harmonization of the hazard assessment in pharma

**Deriving HEALTH-BASED EXPOSURE LIMITS in the PHARMACEUTICAL INDUSTRY**

A workshop was convened to advance harmonization and best practices in ADE/PDE derivation and application.

In pharmaceutical development and manufacturing, health-based exposure limits are established to protect against potential adverse health effects. For many years, the most common application of health-based exposure limits has been for occupational exposure limits (OELs) used to protect workers who manufacture or process pharmaceuticals. OELs can be viewed as derivatives of acceptable daily exposures (ADEs), and a transition to the use of ADEs and permitted daily exposures (PDEs) to protect product quality has gained industry and regulatory interest.

Although there are many different types of manufacturing-related impurities, recent regulatory scrutiny and international guidelines have focused attention on prevention of cross-contamination in equipment or facilities, including residues of active pharmaceutical ingredients (APIs) that may be present in other medicinal products produced subsequently in the same equipment or facility. This interest stems from the fact that APIs by definition have biological activity, and in some cases, at very low doses.

There is a variety of empirical approaches that have been used historically to manage such cross-contamination issues and good manufacturing procedures (GMPs). In general these empirical approaches have not been data-driven methodologies. For example, one approach has included requirements for dedicated facilities for “certain” types of compounds (e.g., certain antibiotics, certain hormones, certain cytotoxics, and other highly active compounds) (ICH, 2001; EMA, 2014a; FDA, 1978).

However, this left to interpretation which compounds required dedicated facilities, and in turn, even the definition of “dedicated”. Other early approaches used to derive product quality limits for shared facilities did not use risk assessment methodologies for health-based limit setting. For instance, limits were proposed based on analytical...
Key thoughts

• PDEs are **good news**: not only for the quality, but also for the occupational risk assessment
  – Because we better collaborate across the industry
  – Because we put emphasis on consistency, data and expertise

• Important to communicate the risks appropriately

• Quality of hazard assessment
  – Think about your family member: **What quality do you expect for them?**
Thank you
References ester.lovsin_barle@novartis.com