



## Is HPAPI also a Low PDE?

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### Prospective

Potency is determined by the dose of the drug required to produce an effect. A highly potent drug (e.g., fentanyl, estrogen, calcitriol) evokes a desired pharmacological response in target population of patients at low concentrations. On the other hand, these drugs may also evoke unintended, adverse effects at doses lower than the intended effects. These effects may be acceptable in the patient population; however they are not acceptable in other populations, such as workers, or patients who would receive such a drug as a contaminant. Due to these differences, defining an HPAPI is not uniform.

The definition of an HPAPI varies significantly in the literature. The following definitions may be found:

1. DS or IM with biological activity at approximately 150 µg/kg of body weight or below in humans (therapeutic daily dose at or below 10 mg).
2. DS or IM with an occupational exposure limit (OEL) at or below 10 µg/m<sup>3</sup> of air as an 8-h time-weighted average.
3. DS or IM with high selectivity (i.e., ability to bind to specific receptors or inhibit specific enzymes) and/or with the potential to cause cancer, mutations, developmental effects, target organ effects or reproductive toxicity at low doses.
4. Or, by default, a novel compound of unknown potency and toxicity [1].

In their GMP guidelines, regulatory agencies sometimes include the following sentence: “The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities.” However they leave the assessment of the definitions for these terms to the individuals.

Permitted Daily Exposure (PDE) is presently not included in the definitions of highly potent or highly active. To understand if a PDE value can be an indicator of a HPAPI, we must understand how the PDEs are derived.

For the purposes of PDE calculation based on toxicological criteria, a critical effect needs to be identified; in this context any effect is an adverse effect, on target or off target. Identification of the

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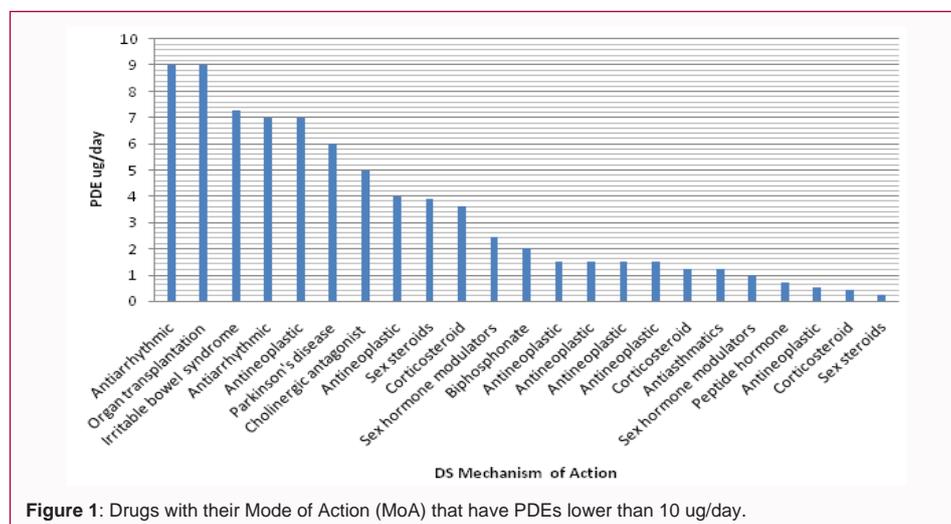


Figure 1: Drugs with their Mode of Action (MoA) that have PDEs lower than 10 ug/day.

**Table 1:** Adjustment factors (AF) typically used in the derivation of PDE for systemically administered drugs. Multiplication of all AFs is termed Composite Adjustment Factor (CAF). Detailed description of the use of these AFs is described in Novartis Global technical best practice document Calculation of the Permitted Daily Exposure (PDE) for drug substances (DS) and intermediates (IM).

Adjustment factors (AF)	Value range	Purpose of the AF
Interspecies variability	1-12	AF needs to be applied to address uncertainties associated with estimating a human equivalent dose from a NOAEL (or LOAEL) derived from animal studies.
Intraspecies variability	1-10	It considers the differences between individuals within an exposed population. The differences may be based on physiological, biochemical or social aspects. A factor of 10 to account for variability between individuals in general population is default value. There a possibility to derive chemical specific adjustment factors (CSAF) on case-by-case basis.
LOAEL to NOAEL	1-10	When only a LOEL is available, a factor of up to 10 could be used in order to extrapolate a NOAEL depending on the severity of the toxicity. Instead, when only a LOAEL is available, a factor of 3 is used to extrapolate a NOAEL.
Duration of exposure	1-10	When the duration of the study used to identify the critical effect is different from the actual exposure scenario, an additional adjustment is set for study duration. As a default a lifetime daily exposure is considered.
Database completeness	1-10	Database completeness factor represents a judgment on the quantity and quality of information available on the toxicological hazards of a substance. A common default in the case of insufficient data is 10, with lower values e.g. 3, or 1 being employed as significant 'gaps' in the available data are filled.
Severity of effect	1-10	It is used to introduce an additional margin of safety when a compound has produced some form of severe, or irreversible toxicity not previously covered by the POD or AF.
Bioaccumulation	1-10	An additional pharmacokinetic adjustment may be needed if a potential for bioaccumulation is identified with repeated exposures.
Bioavailability	0.01-100	Adjustments applied to reflect differences in route-specific bioavailability. In these cases, route-to-route extrapolation is necessary when attempting to derive a PDE from a study conducted by a route (e.g., oral) that is different from the potential route of exposure (i.e., IV). As a general rule, direct studies using the relevant route of administration are preferred.
CAF		Multiplication of all the above factors.

critical effect requires comprehensive evaluation of all relevant data and identifies the no-observed-adverse-effect level (NOAEL) for the critical effect, also termed as point of departure (POD) for the PDE calculation (Figure 1) [2].

$$\text{PDE } [\mu\text{g/day}] = \text{POD } [\text{mg/kg/day}] \times \text{BW } [\text{kg}] \div \text{Composite Adjustment Factor (CAF)} \times 1000$$

OELs are calculated in a very similar way; the critical difference is in the determination of the critical effect for the target population of healthy workers vs. [3,4] patients, followed by modification of AFs to adjust for this criterion. Also the OEL is expressed in  $\mu\text{g}/\text{m}^3$  to extrapolate to the volume of air inhaled in 8h working time ( $10 \text{ m}^3$ ). Therefore OEL (in  $\mu\text{g}/\text{m}^3$ ) is typically 10x lower than a PDE (in  $\mu\text{g}/\text{day}$ ).

Similarly to the OEL PDE values fall into a range that spans over several orders of magnitude. In a study done with over 200 substances in typical pharma portfolio, there were about 66% of drugs with PDE > 100  $\mu\text{g}/\text{day}$ , 36% of drugs with PDE <100  $\mu\text{g}/\text{day}$ . In this dataset, there were 12% of substances with PDE <10  $\mu\text{g}/\text{day}$ , and 2% of drugs with PDE < 1  $\mu\text{g}/\text{day}$ .

In general there are several groups of substances that are already considered HPAPI based on previous criteria, such as low therapeutic dose (eg., peptide hormone oxytocin, guanylate cyclase stimulant for irritable bowel syndrome, dopamine agonists for Parkinson's disease), or drugs that have adverse effects in low doses (eg. certain

genotoxic antineoplastics) or both of these criteria (eg. sex steroids and sex hormone modulators). Table 1 However there are some substances that might have relatively high therapeutic doses, which are not dosed daily (eg. bisphosphonates). These doses must be for the purposes of PDE and OEL calculations extrapolated to daily doses, showing that the therapeutic dose alone is not a good indicator of HPAPI.

## Conclusion

An OEL of 1  $\mu\text{g}/\text{m}^3$  is a good indicator that a PDE value will be under 10  $\mu\text{g}/\text{day}$ , however daily dose may not be.

## References

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