Case Study: Setting HBELs Throughout the Product Life Cycle

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Outline

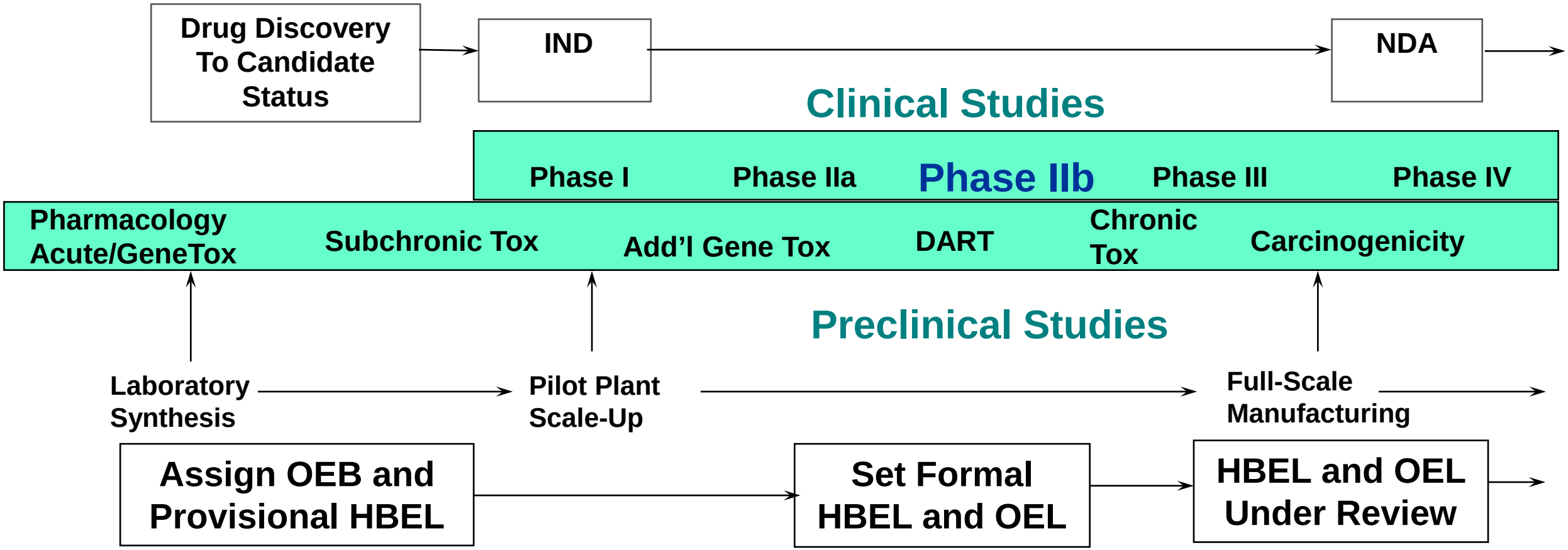
- Provisional HBELs using TTC, OEBs, OELs
- Formal HBEL for a Kinase Inhibitor
- HBEL Monographs
- Key Messages

Health-Based Exposure Limits (HBELs)

A daily dose of a substance below which **no adverse effects** are anticipated, by any route, even if exposure occurs for a lifetime.

Note: EMA considers ADE to be synonymous with PDE

Drug Product Life Cycle



Hazard Continuum and Prioritization for Risk Assessment

HAZARD

Less Severe — **More Severe**

Irritation — **Biochemical Changes** — **CNS Depression** — **Liver Damage** — **Birth Defects** — **Cancer**

Negligible — **Non-Critical Reversible** — **Critical Non-Reversible** — **Terminal**

IMPACT

Hazard Continuum and Prioritization for Risk Assessment

Occupational Exposure Limit (OEL)

>1,000 µg/m³	1,000 µg/m³	100 µg/m³	10 µg/m³	1 µg/m³	<1 µg/m³

>10,000 µg/day	10,000 µg/day	1,000 µg/day	100 µg/day	10 µg/day	<10 µg/day

Health-Based Exposure Limit (HBEL)

Health-Based Exposure Limits (HBELs)

HBELs should be derived by a qualified expert (e.g., experienced toxicologist):

- ✓ Formal training in toxicology or related field (e.g., pharmacology), preferably with higher degree
- ✓ Familiarity with pharmaceuticals
- ✓ **Experience deriving health-based exposure limits (e.g., ADEs, OELs) – multiple years desirable**
- ✓ Certification in Toxicology (e.g., DABT) a plus

Prioritization of Risk* Assessments

Identify compounds based on severity of hazard:

- Genotoxic compounds that are known or likely to be carcinogenic to humans.
- Compounds that can produce reproductive and/or developmental effects at low dosages.
- Compounds that can produce serious target organ toxicity or other significant adverse effects at low dosages.

Identify worst-case exposure scenarios:

*Risk = f(hazard x exposure)

Thresholds of Toxicological Concern

Provides guidance for relatively unstudied compounds that fall into one of three categories:

1) compounds that are likely to be carcinogenic

(ADI = 1 ug/day)

2) compounds that are likely to be potent or highly toxic

(ADI = 10 ug/day)

3) compounds that are not likely to be potent, highly toxic, or genotoxic

(ADI = 100 ug/day)

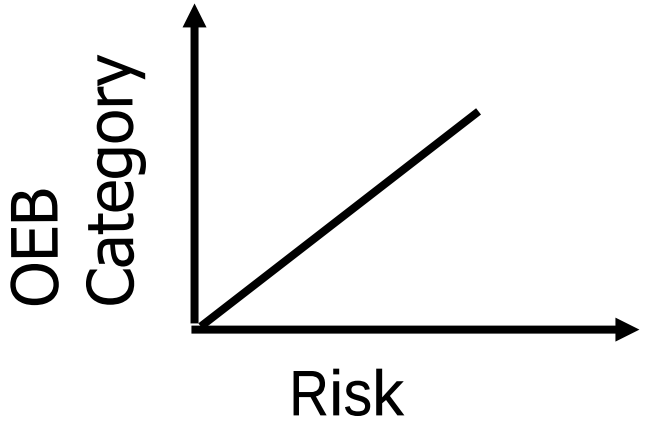
ADI = Acceptable Daily Intake (synonymous with ADE/PDE)

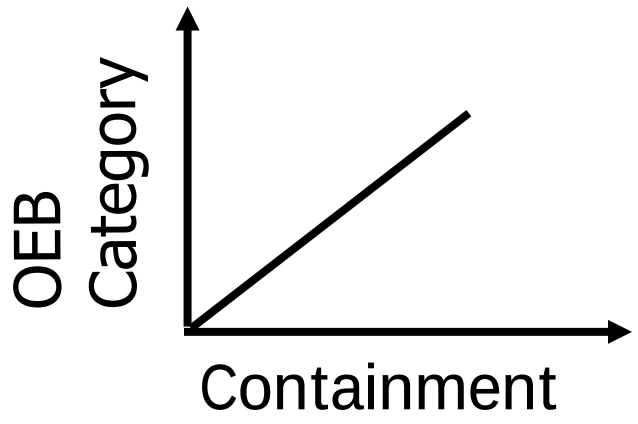
Dolan DG, Naumann BD, Sargent EV, Maier A, Dourson M Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. *Regul. Tox. Pharm.* 43:1-9 (2005).

Note: Stanard et al. 2015 also recommend 1 ug/day for anticancer drugs with potential developmental or reproductive liabilities. ICH M7 recommends 1.5 ug/day for mutagenic impurities.

Occupational Exposure Bands (OEBs)

- A classification system used to assign materials into one of five health hazard categories of increasing severity based upon their inherent pharmacological and toxicological properties.
- These categories also correspond to predefined strategies known to provide the necessary degree of control to protect employees and the environment.





Note: The 5 band system (1-5 OEB) is not universally used and the cut-off values between bands are company dependent.

Setting Provisional HBELs: An Example

Provisional HBEL = Low End of the Band x 10 m^3

OEB	Concentration Range	Low End of the Band	Provisional HBEL
1	≥1<5 mg/m^3	1 mg/m^3	10 mg/day
2	≥0.1<1 mg/m^3	0.1 mg/m^3	1 mg/day
3	≥10<100 µg/m^3	10 µg/m^3	100 µg/day
4	≥1<10 µg/m^3	1 µg/m^3	10 µg/day
5	<1 µg/m^3	<1 µg/m^3	≤1 µg/day

Adapted from : Teasdale, A, Naumann, B.D., Allison, G., Lou, W., Callis, C.M., Shipp, B.K., Rutter, L., Seaman, C. (2016). EMA Guideline on Setting Health-Based Exposure Limits - The results of an industry workgroup's examination of EMA's guide on shared facilities. Pharm. Technol. 40(1). http://www.pharmtech.com/ema-guideline-setting-health-based-exposure-limits

Setting Provisional HBELs Using OELs

$$\text{OEL } (\mu g/m^3) = \frac{\text{PoD (mg/kg/day) x BW (kg)}}{AF_C \text{ x MF x PK x V}}$$

Provisional HBEL* (µg/day) ~ OEL x 10 m^3

*Differences in critical effect, point-of-departure, bioavailability and susceptible subpopulations may influence accuracy of estimate. Therefore, a qualified expert (e.g., experienced toxicologist) should be consulted.

Evaluation of Oncology Drugs

Historically "oncology" was synonymous with cytotoxic, but oncology compounds are now designed to be more specific to a therapeutic target. Categories like "cytotoxics" should no longer be used.

ATTRIBUTES OF "CYTOTOXIC" DRUGS

- Cause cell death due to direct actions on DNA or DNA associated macromolecules, demonstrating or predicted to cause genotoxicity *in vivo*; and
- Cause rapid and non-specific cell death in healthy as well as abnormal cells

ATTRIBUTES OF NOVEL ONCOLOGY DRUGS

- Newer chemotherapeutic agents are, in general, more discriminating in their targets.
- Some target mutated genes that are only present in tumor cells (targeted therapies).
- Others inhibit tumor proliferation by "indirect" mechanisms (i.e., through the modulation of cell signaling pathways).

Sussman, R.G., Schatz, A.R., Kimmel, T.A., Ader, A., Naumann, B.D. (2016). Identifying and assessing highly hazardous drugs within quality risk management programs. *Regul. Toxicol. Pharmacol.* 79, S11-S18, http://www.sciencedirect.com/science/article/pii/S027323001630138 6)

Health-Based Exposure Limit (HBEL): Kinase Inhibitor for Oncology

- Investigational drug used in combination with cytotoxic chemotherapy agents for treatment of cancer.
- Inhibits repair of DNA damage.
- NOAEL=5 mg/kg/day for hematopoietic and liver effects in a 4-week study in dogs.
- Negative in the Ames test (non-mutagenic) but positive in chromosomal aberration study at high concentrations (threshold effect).

Establishing Formal Health-Based Exposure Limits (HBELs)

1. Identify the critical endpoint (i.e., the most sensitive clinically significant health effect)
2. Define the Point-of-Departure (NOAEL, LOAEL, BMD)
3. Consider sources of variability/uncertainty and apply appropriate adjustment factor(s)
4. Calculate a health-based exposure limit (HBEL)

Health-Based Exposure Limit (HBEL): Kinase Inhibitor for Oncology

$$\text{HBEL (ug/day)} = \frac{\text{PoD x BW}}{\text{AF}_C \text{ x MF x PK}} = 20 \text{ ug/day}$$

where:

PoD = Point-of-Departure = 5 mg/kg/day (NOAEL for blood and liver effects)

BW = Body Weight = 50 kg

AF_C = Composite Adjustment Factor = 180

(F1 or AF_A=2, F2 or AF_H=10, F3 or AF_S=3, F5 or AF_L=1, AF_D =3)

MF = Modifying Factor = 10 (residual uncertainties for developmental and genotoxic effects)

PK = Pharmacokinetic adjustments (α=7, S=1)

HBEL Monographs

Documentation of ADEs/PDEs is critical:

- Demonstrates that the product owner has completed an appropriate hazard assessment.
- Provides a scientific rationale for the recommended health-based limit to ensure patient protection.
- Informs and facilitates communication between different operational groups, e.g., engineering and manufacturing groups charged with implementing a quality risk management program elements, e.g., cleaning validation.
- Facilitates communication with external partners and regulators.

HBEL Monographs

Should be able to readily determine:

- The health endpoint (critical effect) on which the ADE/PDE was established.
- Values chosen for adjustment factors, and which sources of variability and uncertainty they address.
- Any further adjustments (e.g., bioavailability correction).

Key Messages

- The evaluation of risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient (ICH Q9).
- A toxicological evaluation and establishment of a health-based exposure limit (HBEL) is a key step in a quality risk assessment.
- The HBEL should be established by a qualified expert (e.g., experienced toxicologist).
- Toxicologists use all available relevant data and well-established limit setting methods.
- The HBEL is a conservative value.

Key Messages

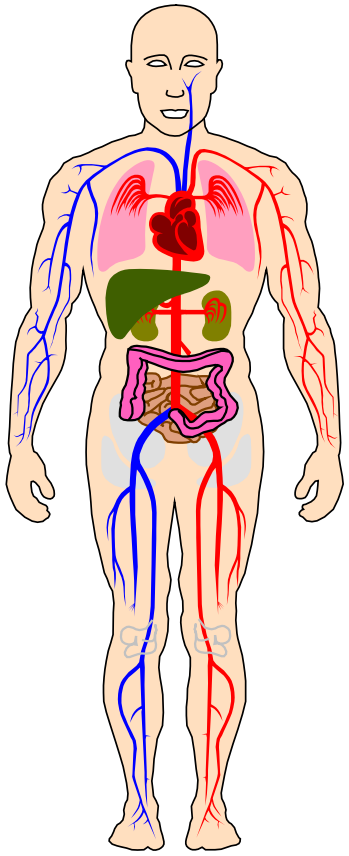
- An HBEL should be established for all compounds where the data permit, including hormones and oncology drugs.
- Provisional HBELs can be derived using OEBs, OELs and Threshold of Toxicological Concern (TTC) values for prioritization of risk assessments and for early development compounds.
- The rationale for the HBEL should be well-documented.
- The level of effort, formality and documentation of the quality risk management process [*including the toxicological evaluation]* should be commensurate with the level of risk (ICH Q9).

Back-Up Slides

Identification of the Critical Effect

Preclinical and Clinical Data:

Pharmacology/Mode-of-Action
Acute Toxicity/Dose-Limiting Toxicity
Local Tolerability/Sensitization
Subchronic/Chronic Toxicity
Reproductive/Developmental Toxicity
Mutagenicity/Genotoxicity/Carcinogenicity
Human Safety/Efficacy



Adjustment Factors*

- Interspecies Extrapolation
- Interindividual Variability
- Study Duration
- LOAEL-to-NOAEL Extrapolation
- Database Completeness
- Modifying Factor for Residual Uncertainties and Severity of Effect
- Pharmacokinetics, Route-to-Route Extrapolation

* Also referred to as Safety or Uncertainty Factors

Factor	EMA	Risk-MaPP	Comment
Interspecies	F1 = 2-12	AF_A = 2-12	$BW^{2/3}$ or $BW^{3/4}$
Intraspecies	F2 = 10	AF_H = 10 or CSAF	Use PK and PD Data
Study Duration	F3 = 10	AF_S = 3	< 4 weeks
Severity of Effect	F4 = 1-10	MF in update	Overlaps with F5; MF
LOAEL-to-NOAEL	F5 $\leq$ 10	AF_L = 3	F5 = 10 if severe effects
Database Completeness	AF=10 or Read Across	AF_D = 1-10	Missing Repro Data
Modifying Factor	MF	MF $\leq$ 1-10	Residual Uncertainties
Pharmacokinetic Adjustments	Bioavailability Correction	Bioavailability Correction (α), Steady State (S)	Route-to-Route Extrapolation

HBEL Monographs

Document should include:

- Summary of ADE/PDE derivation to facilitate review by stakeholders
- Identity information, physico-chemical properties, and chemical structure
- Intended use and mechanism of action
- Pharmacokinetics and pharmacodynamics
- Animal data including acute toxicity, local effects, repeat-dose toxicity, developmental and reproductive toxicity, genotoxicity, carcinogenicity

HBEL Monographs

Document should include (cont.):

- Human data including pharmacokinetics, clinical use, adverse reactions, susceptible sub-populations, pregnancy and nursing mothers
- Identification of the critical effect
- Basis for the ADE/PDE with adjustment factors
- References
- Qualifications of the monograph author,
- Appendices that provide further details, e.g., equations showing the calculation of the ADE/PDE, chemical-specific adjustment factors (CSAFs), etc.