Proactive Integration of Occupational Toxicology Assessments into the Drug Development Process

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The topics covered in this presentation include:

How AbbVie establishes Estimated Limit Summaries (ESTLs) for urgent and early development needs

Performance Based Limit of Exposure Control (PBLEC), CHAP Code, Residual Dose Level (RDL)

Risk assessment and general process to establish limits

* ICH Q9 as a framework

* RiskMaPP - Risk-based Manufacture of Pharmaceutical Products

Basic Concepts and Definitions

Implementation of RiskMaPP-based approach for establishment of health-based occupational exposure limits. How AbbVie establishes Employee Exposure Limits (EELs) and Residual Dose Limits (RDLs) using the RiskMaPP approach

General Formula and Example calculation

Facility and equipment requirements (shared, dedicated, disposable equipment, etc.)
ICH Q9 outlines a process to determine acceptable risk

Establishing exposure limits is a risk assessment process, not a risk management process.
Performance-Based Limit of Exposure Control (PBLEC)

• A classification system used to assign materials into a series of 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.

• Now referred to as Control Bands or Occupational Exposure Bands (OEBs)

Performance-Based Limit of Exposure Control (PBLEC)

• Alternate to EELs for pre-clinical drugs

• Uses semi-quantitative data to establish biological safety containment levels (e.g., 1S - 4S) to control employee exposures

• RDLs will still be established using ESTL process using a default ultra-conservative process

• PBLEC is replaced when an EEL is established
Estimated Limit Summaries (ESTLs)

- ESTLs are often the first limit summary documents written for occupational exposure assessment.

- ESTLS are used in early development to establish limit parameters (PBLEC, CHAP Code and RDL) for starting materials, intermediates and APIs for the entire synthetic scheme. More formal, toxicology data rich documents are authored later in API development (formal limit summary EEL/OEL and RDL)

- Assign PBLEC 2 category with a default RDL of 100 mcg/day.

- Assign PBLEC 3 category with a default RDL of 10 mcg/day.

- Assign PBLEC 4 category with a default RDL of 1.5 mcg/day (aligns with the TTC) for highly-potent APIs.

- PBLEC 4 category = an OEL <1 mcg/m3 8H TWA for OEL with the action limit of 0.5 mcg/m3 (EHS action level is 50% of the OEL value).
Building the ESTL document

• ESTL authored in WERCS (Worldwide Environmental Regulatory Compliance System) software system. Early development API, intermediate or starting material has no toxicity data available, only a chemical structure

• SciFinder software used to find structurally similar compounds to possibly use as an analogy to the API to predict toxicity potential of the API. Can also use other systems (e.g., ChemDraw and ChemIDPlus)

• Search toxicology databases for available toxicity data for the identified structurally-analogous compound(s) (preference ≥ 80% similarity)

• Have ESTL reviewed at the scheduled monthly AbbVie Drug Handling Committee (ADHC) if not urgent or if is an urgent business need, send ESTL in an attachment in an e-mail to the ADHC and request review/comments/vote within no more than 48 business hours.
What is RiskMaPP?

Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP)

- It provides a scientific risk-based approach to the production of pharmaceuticals that balances:
  - Product quality
  - Employee safety

Risk Identification – RiskMaPP Process

• Includes Acceptable Daily Exposure (ADE) development Process:

Identification of hazards

- APIs
- Intermediates
- Starting materials

• Assessment of the dose-response relationship

• Calculation of the ADE

• Establishment of health-based limits – Set by the Toxicologists based on the ADE and approved by the AbbVie Drug Handling Committee (ADHC)

• Estimated Limit (ESTL) and Performance Based Limit of Exposure Control (PBLEC); Employee Exposure Limit (EEL); Residual Dose Level (RDL)
Why Use the RiskMaPP and Health-Based Limits?

• All compounds represent a hazard.

• Highly hazardous compounds can produce toxic effects.

• Lowering exposure to a hazard lowers the risk of an adverse effect.

• Operational controls are required to minimize cross-contamination and to minimize risks.

• Exposure to “highly hazardous” compounds should be maintained below the health-based limit.
• Data from regulatory filings or literature are used to establish the acceptable daily exposure (ADE) or equivalent (RDL).

• When developing the health-based limits, all health endpoints are addressed by toxicologists.

• Well-established limit setting methods are used to derive ADEs or equivalent health-based limits (RDL).

• The use of the health-based limits as the basis for risk assessment in the manufacture of pharmaceutical products is a scientifically sound approach.
Setting limits using RiskMaPP Principles

- RiskMaPP defines a scientifically-based, systematic approach for setting health-based limits that uses the following:
  - Identification of the critical end point (i.e., the most sensitive clinically significant health effect)
  - Define the NOEL/NOAEL or LOEL/LOAEL
  - Consideration of sources of uncertainty and appropriate choice of “safety factor(s)”
  - Calculation of an Acceptable Daily Exposure (RDL based on ADE)
Process of 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
- Common Side Effects/Adverse Reactions
Application of Uncertainty (Safety) Factors

- Interindividual Variability – (UFH) Default of 10 or Data-derived
- Interspecies Extrapolation – (UFA) Allometric Scaling (BW2/3 or 3/4) or Chemical specific adjustment factor (CSAF)
- LOEL-to-NOEL Extrapolation – (UFL= Default of 3)
- Subchronic-to-Chronic Extrapolation – (UFS= Default of 3)
- Route-to-Route Extrapolation – CSAF
- Data Based Quality and Completeness – (UFD = Range of 1-10)
- Modifying Factor used for Additional Uncertainties – (MF = Range of <1-10)

Establishing Health-Based Limits: Acceptable Daily Exposure (ADE)

ADE (mg/day) = \frac{\text{NOAEL (mg/kg/day) x BW (kg)}}{\text{UFC x MF}}

where:

ADE = Acceptable Daily Exposure

NOAEL = No-Observed-Adverse-Effect Level

BW = Body Weight (kg) [default for an adult is 50kg]

UF_C = Uncertainty Factor(s)

MF = Modifying Factor

UF_H = Interindividual variability = 10 (to account for variability between individuals)

UF_A = Interspecies extrapolation

\alpha = Absorption (bioavailability) Correction Factor (1/F)
Setting Health-Based Safety Thresholds/Acceptance Limits

How are ADEs Used?

Cleaning Limits:

- Residual Dose Levels
- Swab Limits (product contact surfaces)
- Rinse Limits

Occupational Exposure Limits:

- Airborne Limits
- Wipe Limits (workplace cleanliness)
Thresholds of Toxicological Concern and Setting an ADE (RDL) Value

Provides guidance for setting an ADE (RDL) for relatively unstudied compounds that fall into one of three categories (Examples only) since containment category (PBLEC or S-category is based on WOE):

1) compounds that are likely to be genotoxic and/or carcinogenic.
   
   (ADE = 1.5 mcg/day)

2) compounds that are likely to be potent or highly toxic.
   
   (ADE = 10 mcg/day)

3) compounds that are not likely to be potent, highly toxic, or genotoxic. (ADE = 100 mcg/day)

RDL (Cleaning Limits) and Safety Margins based on Therapeutic Dose

<table>
<thead>
<tr>
<th>PBLEC</th>
<th>RDL (mcg/day)</th>
<th>1 mg</th>
<th>10 mg</th>
<th>100mg</th>
<th>1,000mg</th>
</tr>
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<tbody>
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<td>1 and 2</td>
<td>100</td>
<td>10x</td>
<td>100x</td>
<td>1000x</td>
<td>10,000x</td>
</tr>
<tr>
<td>3</td>
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<td>100x</td>
<td>1,000x</td>
<td>10,000x</td>
<td>100,000x</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>667x</td>
<td>6,667x</td>
<td>66,667x</td>
<td>666,667x</td>
</tr>
</tbody>
</table>
Establishing Limits

• Establishing chemical exposure limits is a risk assessment process, not a risk management process

• Collect and evaluate physical - chemical, human and animal data

• Apply RiskMaPP based approaches tailored to data available and to type of material:
  • Assessment of clinical data - pharmaceuticals
  • Assessment of animal data - chemicals and pharmaceuticals
  • Assessment of special data - unique materials

• Limit generally dose driven with modification based on:
  • Severity of effect (e.g., headache vs. tissue damage)
  • Type and quality of data
  • Special concerns
Employee Exposure Limits (EEL) or OEL

\[
EEL \ (\text{mcg/m}^3) = \frac{\text{NOAEL} \times \text{BW} \times 1000 \ (\text{mcg})}{\text{UFc} \times \text{MF} \times V \times \alpha}
\]

where:

NOAEL = No Observed Adverse Effect Level (mg/day). If human low clinical therapeutic dose is known, it is considered as LOEL and used in the EEL derivation, and BW is not accounted.

\(\text{BW} = \text{body weight (kg)} \ [\text{default for an adult is 50kg}]\)

\(\text{UFc} = \text{uncertainty factor (composite)}\)

\(\text{MF} = \text{Modifying Factor (professional judgment)}\)

\(V = \text{Volume of air breathed (10 m}^3\) in eight hours\)

\(\alpha = \text{Absorption (bioavailability) Correction Factor (1/F)}\)

Example of Limit Setting Process - EEL Determination for Timolol Maleate (a non-selective beta blocker)

\[ \text{EEL (mcg/m3)} = \frac{\text{LOAEL} \times 1000}{\text{UF}_C \times \text{MF} \times \text{V} \times \alpha} = 15 \text{ mcg/m3} \]

where:

- \( \text{LOAEL} \) = Low-observed-adverse-effect level (mg/day) = 10 mg
- \( \text{UF}_C \) = uncertainty factors composite\([\text{CSAF (11)xUFL(3)}]\) = 33
- \( \text{UF}_L \) = LOAEL to NOAEL = 3
- \( \text{MF} \) = Modifying Factor (professional judgment) = 1
- \( \text{V} \) = Volume of air breathed (10 m\(^3\)) in eight hours
- \( \alpha \) = Absorption (bioavailability) Correction Factor (1/F) = 2

Based on the calculations above = Recommended EEL = 15 mcg/m\(^3\) 8-hour TWA.
Special Case Considerations

- Short-term limit (dose-rate for rapidly acting drugs)
- Threshold for drug’s biological activity
- Material naturally occurring in body
- Material needed by the body (e.g., vitamins)
- Dedicated equipment for penicillins and cephalosporins
- Limits for foreign (non-human) protein
- Severe irritation/corrosion - 10 mcg/m³ 8-hour TWA default to limit irritation unless data indicate smaller EEL necessary (e.g. <1 mcg/m³)
- Sensitizer notation
- Biological monitoring/medical surveillance
Calculating Residual Dose Limits (RDL)

\[
RDL \text{ (mcg/day)} = \frac{\text{NOAEL (mg/kg/day)} \times \text{BW (kg)} \times 1000 \text{ (mcg)}}{\text{UFC} \times \text{MF}}
\]

where:

- \( RDL \) = Residual Dose Level
- \( \text{NOAEL} \) = No-Observed-Adverse-Effect Level
- \( \text{BW} \) = Body Weight (kg) [default for an adult is 50kg]
- \( \text{UFC} \) = Uncertainty Factor(s)
- \( \text{MF} \) = Modifying Factor (professional judgement)

Note: If human low clinical therapeutic dose is known, it is considered as LOEL and used in the RDL derivation, and BW is not accounted.
Example of Limit Setting Process – RDL Determination for Opioid Analgesic

RDL (mcg/day) = \frac{\text{LOAEL (10mg/day)} \times 1000}{\text{UFC (90)} \times \text{MF (1)}} = 100 \text{ mcg/day}

where:

RDL = Residual Dose Level

LOAEL = Low-observed-adverse-effect level (mg/day) = 10 mg

UFC = uncertainty factors composite [CSAF (30) \times UF_L (3)] = 90

UFL = LOAEL to NOAEL = 3

MF = Modifying Factor (professional judgment) = 1
Hazard Continuum and Prioritization for Risk Assessment

- Less Severe
  - Irritation
  - Biochemical Changes
  - CNS Damage
  - Liver Damage
- More Severe
  - Birth Defects
  - Cancer
Formal Limit Summary (EEL and RDL) vs ESTL

- ESTLs contain the PBLEC category, CHAP Code and RDL value and generally have no toxicity data available for the compound. Therefore, conduct a structural-similarity analogy (e.g., SCiFinder, ChemDraw, ChemIDPlus-free access) to the actual chemical compound when data are not yet available to allow a formal RiskMapp limit (EEL or RDL) to be derived.

- ESTLs established only by groups (e.g., occupational toxicologists) designated by ADHC under signature of chairman with oversight of ADHC.

- ESTLs not subject to 5-year ADHC review process; however, they can be retired and/or archived when formal EEL and RDL values are able to be derived (e.g., at the clinical Phase 2B milestone).

- ESTLs may have large safety margins as they are based upon limited data, or analogy; however, EELs and RDLs are subject to the RiskMaPP process. Typical margin of safety $\geq 30$. 
Some Possible Scenarios:

- Shared facility with shared equipment and clean to below the RDL value (e.g., 1.5 mcg = aligns with the TTC).
- Shared facility with dedicated equipment and clean to below the RDL value.
- Dedicated facility with shared equipment and clean to below the RDL value.
- Dedicated facility with dedicated equipment and clean to below the RDL value.
- Dedicated facility with dedicated equipment and use disposables (e.g., reactor liners).
Summary

The process used by the AbbVie Drug Handling Committee (ADHC) to set estimated limit summaries (ESTLs), employee exposure limits (EELs) and residual dose limits (RDLs) are a risk assessment, not a risk management process.

The evaluation is a RiskMaPP based approach on all available data including chemical, animal and human information but the emphasis is on clinical data for pharmaceuticals, on animal data for chemicals and pharmaceuticals, any special data like sensitizers for unique materials and highly potent compounds.

The employee exposure limit (EEL) and residual dose limit (RDL) are modified based on severity of effects (clinical, target organ effects, etc.), type and quality of the data and any special concerns.

The limit based on the RiskMaPP allows for the provision to manage the risk of cross contamination in order to achieve and maintain an appropriate balance between product quality and operator safety.

The outcome is a scientific risk-based approach, a process which is subject to compliance with cGMP requirements.