



Procedures for Determining an Acceptable Daily Exposure (ADE) under Risk-MaPP: Approaches for Developing and Documenting Acceptable Limits for Product Cross-Contamination Purposes

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Abstract

From a product safety perspective, multi-purpose pharmaceutical and chemical plant manufacturing operations need to be able to adequately clean product contact surfaces, in order to prevent contamination from one product to the next. Contaminants may include active pharmaceutical ingredients (APIs), cleaning agents, decomposition products, synthetic intermediates, excipients, or other residues. Previous approaches in the pharmaceutical and biotechnology industries have been to establish safe or acceptable limits based on a percentage of the human therapeutic dose or of the lethal dose in laboratory animals. More scientifically supportable health-based risk assessment approaches have recently been issued by the International Society for Pharmaceutical Engineering (ISPE) under their Baseline Guide[®] Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP). The following paper describes the procedure employed to establish an Acceptable Daily Exposure (ADE) and the scientific rigor needed to establish defensible ADE values.

Introduction

The ISPE Baseline Guide[®] Risk-MaPP provides a scientific risk-based approach, based on the International Conference on Harmonization (ICH) Q9 Quality Risk Management guidelines, to manage the risk of potential cross contamination in production of active pharmaceutical ingredients and pharmaceutical products. Under Risk-MaPP, a health-based and scientifically supportable risk assessment is performed to establish an Acceptable Daily Exposure (ADE). The ADE may be used as the basis for the maximum amount of API or other material that may be present in the next product. Establishing an ADE for this purpose requires scientific rigor and robust methodology and includes:

- Reviewing relevant toxicological and clinical data available on the API;
- Choosing an appropriate “point of departure” or “critical effect” for the risk assessment
- Using sound scientific judgment to select doses (either from animal or human studies) at the lowest-observed-adverse-effect level (LOAEL) or no-observed-adverse-effect level (NOAEL);
- Employing appropriate risk assessment methodologies, including the selection of defensible safety factors for non-carcinogenic effects or low dose extrapolation for carcinogenic effects; and
- Providing scientifically defensible and transparent documentation supporting the rationale for deriving the ADE.

The Risk-MaPP approach to developing and documenting ADEs will allow drug innovators and suppliers to submit well researched and scientifically sound risk assessment arguments capable of withstanding peer review and regulatory scrutiny.

ADE as a Health-Based Risk Assessment

The ADE represents an estimate of a daily exposure that is likely to be without an appreciable risk of deleterious effects to the potential patient population during an average lifetime. The concept of the ADE is similar to limits developed by other regulatory or authoritative bodies (as well as individual manufacturers) to define “safe” or “acceptable” limits. For example:

- The FAO/WHO sets Acceptable Daily Intakes (ADIs) for additives and pesticide residues in food;
- The US Environmental Protection Agency (EPA) sets Reference Concentrations (RfCs) or Reference Doses (RfDs) as acceptable levels for the general public by inhalation or by oral route of exposure;
- The International Conference on Harmonization (ICH) Q3 Guidelines on Residual Solvents describes the Permissible Daily Exposure (PDE);
- The US Agency for Toxic Substances and Disease Registry (ATSDR) determines Minimum Risk Levels (MRL) as acceptable limits to potentially exposed individuals to contaminants at hazardous waste sites; and

Pharmaceutical and chemical companies establish Occupational Exposure Limits (OELs) for worker safety purposes. An ADE is expressed as mg (or µg) per day, and may consider sensitive subgroups (e.g., elderly and children) potentially exposed to contamination from a drug in a prior batch or product. Once calculated, the ADE can then be employed to establish cleaning limits for equipment and processes used to make the API or drug product. In order to verify that the ADE is not exceeded, the cleaning limit should take into account the dose of the drug in the next batch, the total product contact surface of the equipment, and the total batch size.

ADE Equation

For non-carcinogenic chemicals, the values listed above have typically been determined using a common approach; selecting a NOAEL (mg/kg/day) and applying safety or uncertainty factors to establish the level. ADEs are calculated in a similar manner using the following formula:

$$\text{ADE} = (\text{NOAEL} \times \text{BW}) / (\text{UF}_C \times \text{MF} \times \text{PK})$$

where:

BW	=	Body Weight (kg) [default for an adult is 50 kg];
UF _C	=	Composite Uncertainty Factor;
MF	=	Modifying Factor; and
PK	=	Pharmacokinetic Adjustment(s).

In cases where a NOAEL is not available, a LOAEL may be used. In the event that a human dose is used in a derivation, the NOAEL (or LOAEL or Lowest Therapeutic Dose) may be expressed as mg/day and the BW factor becomes unnecessary. Where sufficient study data are available, other risk assessment approaches may be used, such as extrapolation from known responses at “benchmark doses” to pre-defined levels of risk (e.g., 1:100,000) for carcinogens or applying Thresholds of Toxicological Concern (TTC) for genotoxicants. In many cases, determining the LOAEL or NOAEL requires significant scientific judgment and interpretation of complex non-clinical toxicology and/or clinical studies.

Sources of Uncertainty

A composite uncertainty factor is applied to the NOAEL/LOAEL to account for sources of uncertainty, such as: Intraspecies Differences (interindividual variability) (UF_H);

Interspecies Differences (UF_A);

Subchronic-to-Chronic Extrapolation (UF_S);

LOAEL-to-NOAEL Extrapolation (UF_L); and

Database Completeness (UF_D).

Additional modifying factor(s) may be used in cases when there is potential for bioaccumulation with repeated exposure, or for other variables not included in the above examples. Pharmacokinetic factors may also be considered to adjust for differences in bioavailability by a specific route of exposure.

ADE Development Process

The process of determining an ADE is defined in the Risk-MaPP guideline by three primary steps:

Identification of the hazard

Assessment of the dose-response relationship

Calculation of the ADE

Hazard Identification

In order to identify the most relevant hazard related to a specific compound, the first step is to perform a comprehensive review of readily available animal and human data. The data set will differ depending upon whether the drug is a novel compound in development, a proprietary drug in commercial production, or a generic drug. The following references should be evaluated and obtained specific to the substance of interest or the class of drug substances:

General toxicology and pharmacology references

Medical and toxicology subscription databases and web sites

Drug Innovator's website or Drug Innovator's Clinical Investigator brochure or toxicology summary for a research compound

National Library of Medicine literature search engines

National Drug Agency websites

Once all the literature has been assembled, it should be carefully reviewed. This review may lead to the discovery of additional relevant references to be retrieved and reviewed as well. The goal of this process is to determine the clinical or toxicological endpoint(s) of the drug which will serve as the critical effect for establishing the ADE. Intended pharmacological responses are considered adverse when they occur outside of treatment. For example, reduction of blood pressure by an anti-hypertensive is considered beneficial for the hypertensive individual. However, this same effect may be considered adverse in a normotensive person. Human studies are generally preferred for the selection of the reference endpoint, but animal studies may be used when human studies are limited or if professional judgment indicates that they are more relevant for a particular endpoint. Critical effects that are used as pivotal studies in the risk assessment should be traced back to their original references and verified for the accuracy of their descriptions, findings, and interpretations.

Dose-Response Assessment

Once the critical endpoint(s) are determined, an assessment of the dose-response relationship is performed. As the dose of most drugs increases, so should the incidence and severity of adverse effects. In the ideal study, both a LOAEL and NOAEL will have been established for threshold effects. However, for non-threshold effects, such as cancer, a pre-defined level of acceptable risk should be determined in advance.

ADE Calculation

After selecting a critical effect, uncertainty factors are applied to calculate an ADE. Sources of uncertainty as enumerated in Section 4 usually range from 1 to 10. However, values outside of that range may be used, when appropriate. More than one endpoint may be chosen as a critical effect and leading to multiple calculations. It is not always necessary to select the most conservative limit as the ADE. Often, the limit with the fewest sources of uncertainty is more appropriate. Each calculation should be evaluated for relevance to patient health and appropriateness to the route of exposure, in order to establish a final health-based value.

Documenting the ADE Derivation

In order to provide transparency in ADE derivations, it is essential to prepare a robust monograph to document the process. The monograph should include a summary of the relevant data, detailed derivation of the ADE (including selection of the critical endpoint, NOAEL/LOAEL, and uncertainty factors), and conclusions on the final selection of the value to be used as the ADE. The derivation of these numbers requires a significant amount of professional judgment and peer review and the process of selecting appropriate endpoints and values for the calculations is based on the available data and techniques of current toxicological convention. Therefore, it is essential that manufacturers develop defensible ADE monographs to support their cleaning validation programs.

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