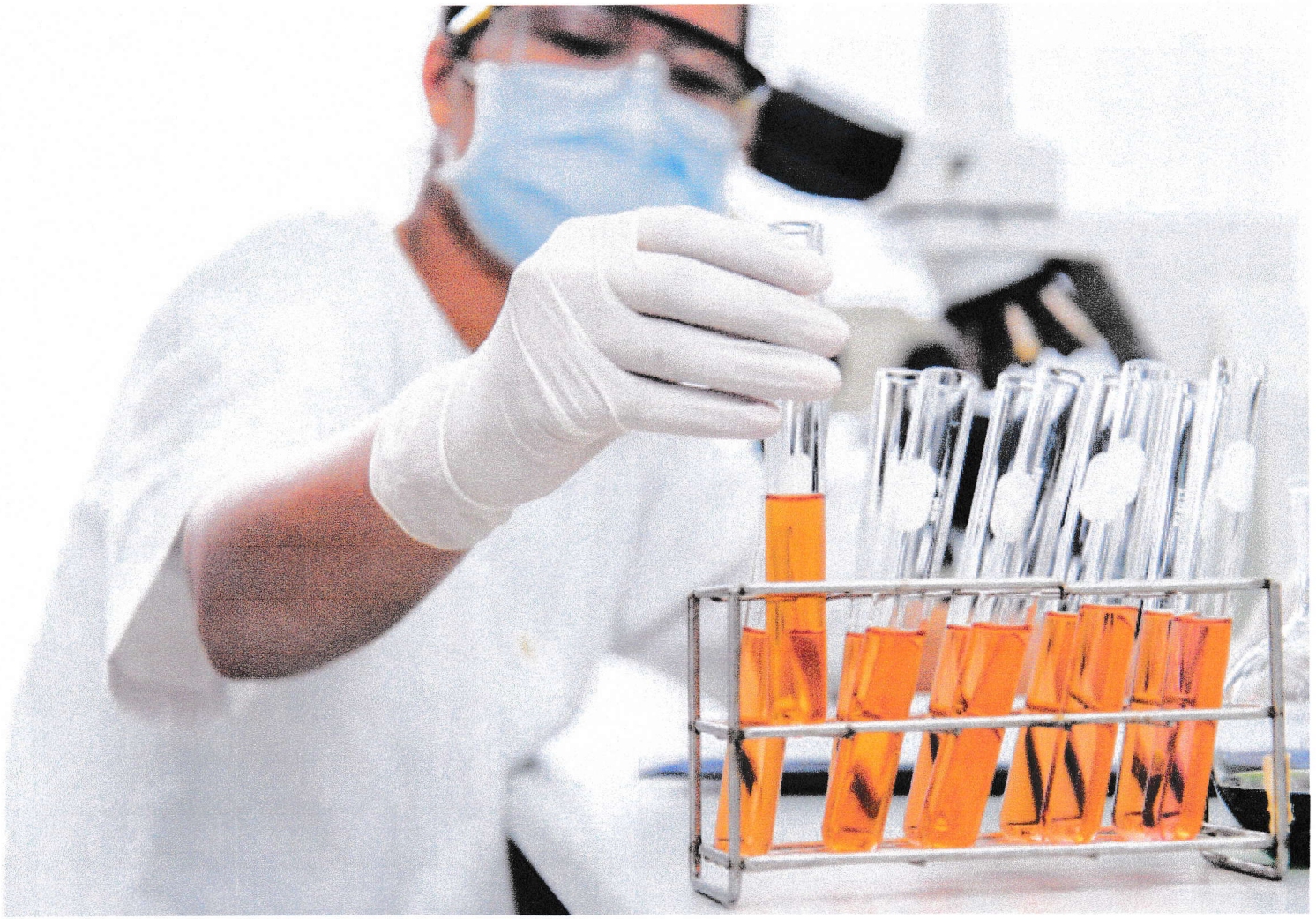


# Deriving HEALTH-BASED EXPOSURE LIMITS in the PHARMACEUTICAL INDUSTRY

**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 guidances 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.

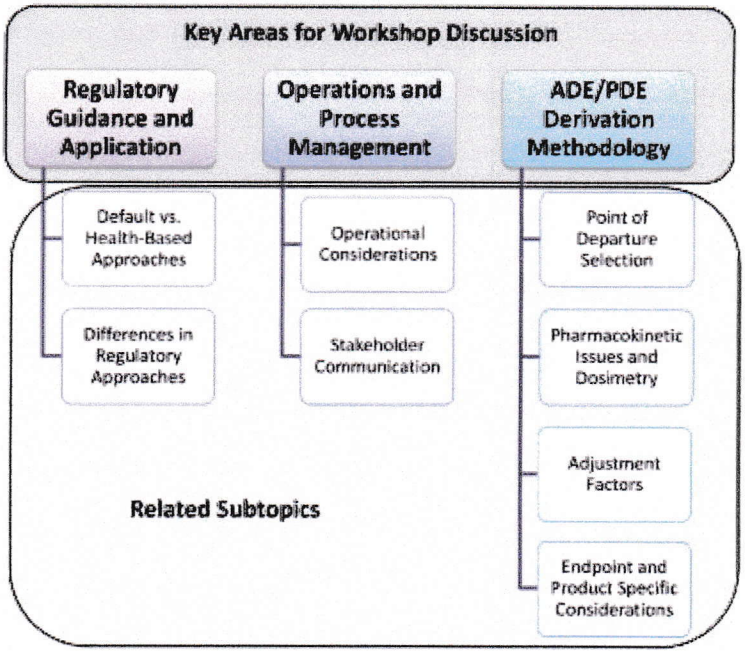
There is a variety of empirical approaches that have been used historically to manage such cross-contamination issues and good manufacturing procedures (GMPs). In general these empirical approaches have not been data-driven methodologies. For example, one approach has included requirements for dedicated 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

detection levels (e.g., 10 ppm), organoleptic levels (such as visibly clean), a predefined fraction of the median lethal dose (LD50) or therapeutic dose (TD), or 1/1,000th of minimum therapeutic dose or lowest clinical dose (LCD) (e.g., Fourman and Mullen, 1993). Such approaches are contrasted to those with a scientific basis for the determination of safety (ISPE, 2010) as discussed below.

## SETTING LIMITS FOR APIS

To address the issue of how to set health-based exposure limits for APIs in multiproduct facilities, two recent guidance documents have been published: the International Society of Pharmaceutical Engineers (ISPE) Risk-MaPP Baseline Guide (2010) and the European Medicines Agency (EMA) Guideline (2014a) on the manufacture of medicinal products in shared facilities. Both of these guidances advocate the use of systematic, scientifically defensible, and health-based approaches for deriving acceptable exposure limits. These guidances build on the approach for derivation of a PDE as outlined in the International Conference on Harmonisation (ICH) guidances for the control of impurities (residual solvents and elements) and degradants in drug product manufacturing (ICH, 1997, 2006a, 2006b, 2011; and reviewed in Dolan et al., 2005; Sargent et al., 2013).




Key Areas for Workshop Discussion

Although the EMA and Risk-MaPP guidances differ in terminology (EMA uses PDE, similar to ICH, and Risk-MaPP uses ADE; EMA defines ADE as 'allowable' daily exposure instead of 'acceptable' daily exposure), both approaches aim to define the "estimated dose that is unlikely to cause an adverse effect if an individual is exposed to the API at or below this dose every day for a lifetime" (ISPE, 2010). The terms ADE and PDE are considered effectively synonymous by multiple parties and agencies (Sargent et al., 2013; EMA, 2014a).

Even though there are some differences between these guidances related to deriving the exposure limit, both approaches include the following steps: 1) review of relevant human, animal, in vitro, and in silico data for hazard characterization; 2) identification of critical (i.e., the most sensitive or relevant) effect(s); 3) selection of the point of departure (PoD) such as a no- (or lowest-) observed-adverse-effect level (e.g., NOAEL or LOAEL); 4) calculation of the ADE/PDE by application of adjustment factors (also called uncertainty factors, assessment factors, safety factors, etc.), dose adjustments based on pharmacokinetic consideration for dosing regimens, and human body weight; and 5) transparent documentation of the supporting rationale for decisions made at each step (Sargent et al., 2013).

There has been an evolution of GMP guidance for use in exposure limit setting and the management of cross-contamination since this issue was first addressed by regulatory agencies over 50 years ago (FDA, 1965). Amendments to drug regulations for current GMPs were published for the control of cross-contamination by penicillin (FDA, 1965). Various guidances and regulatory requirements have been adopted and adapted over the years by multiple organizations, enabling notable differences among regional authorities. ICH has made significant attempts at global harmonization of risk assessment methodologies in the areas of safety, quality, efficacy testing, impurities in general, and mutagenic impurities in particular (ICH, 1997, 2000, 2001, 2005, 2006a,b, 2011, 2014; as reviewed in Dolan et al., 2005; Snodin and McCrossen, 2012; Sargent et al., 2013).

Global harmonization will help to specifically address consistency across companies and agencies, in light of the international character of the manufacture of pharmaceuticals. For example, both the Risk-MaPP and EMA Shared Facilities guidances build on the work of previously published pharmaceutical impurity guidances that also advocate for the use of chemical-specific health-based data for setting pharmaceutical impurity limits. These guidances, in turn, expand on earlier methodologies for setting OELs or PDEs, first-in-human doses for pharmaceuticals, acceptable or tolerable daily intakes (ADIs or TDIs) for additives and/or contaminants in food and/or drinking water, and reference doses and concentrations (RfDs, RfCs) for chemicals of environmental concern (Table 1). A clear need for alignment and consistency is readily apparent and recent attempts at harmonization have been conducted for a number of key areas (Dolan et al., 2005; Dourson and Parker, 2007; Naumann et al., 2009; Walsh, 2011a, 2011b; Snodin and McCrossen, 2012; Bercu et al., 2013).

While progress has been made on using scientifically defensible, health-based methods for setting exposure limits, significant work remains. Existing guidances leave many areas ambiguous, which may ultimately lead to variability in the limits derived, even for the same drug, by risk assessors and/or implemented among companies (Walsh et al., 2013; Walsh, 2011a, 2011b; Snodin and McCrossen, 2012). This has several implications including the erosion of confidence in the limits derived, increased cost of manufacturing, or, at worst, risk to human health.

However, it is important for all to understand that just as there is no single "correct" OEL, there is no single "correct" ADE value. Some variation in ADE/PDE values may be expected based on different parameters, such as PoDs (e.g., based on a pharmacologic NOAEL identified in a proprietary, Phase 1 study, by the innovator company versus

an estimated NOAEL based on a low clinical dose by a generic manufacturer), adjustment factors, and estimation methods (e.g., NOAEL approach vs. benchmark dose approach) by qualified toxicologists.

For example, an innovator company may have a larger ADE value as its more comprehensive clinical and nonclinical testing data may permit a more accurate estimate of a PoD and the use of smaller adjustment factors. On the other hand, generic or contract manufacturers often need to estimate the PoD based on some limited testing data augmented with literature values. As a result, this greater uncertainty due to dataset completeness will drive the use of larger adjustment factors and consequently lower ADEs. However, regardless of dataset, ADE values must be developed by qualified toxicologists or equivalent experts in the ADE assessment process from either innovators' or generic manufacturers' to be protective of patient health.

## THE WORKSHOP

A workshop was convened in October 2014 to identify and address further opportunities for advancing harmonization and best practices in ADE/PDE derivation and application. This workshop brought together toxicologists and other risk assessment scientists from pharmaceutical industries, consulting groups, and academia. The objectives of the workshop were to: 1) provide an open and neutral forum for the discussion of current approaches to deriving ADE/PDEs; 2) evaluate inconsistencies across guidances; 3) identify key areas for harmonization; and 4) document best practices for risk assessment of pharmaceuticals.

This specific language was important because "harmonization" refers to a shared understanding of methods, applications, and their uncertainties. Harmonization in the context of the workshop was not aimed at developing standardized or simplistic prescriptive schemes, or to restrict groups from using methods that best utilize the science and meet their organizational needs.

The workshop originated with a critical analysis of available risk assessment methods used for ADE/PDE setting and the implementation of such limits for pharmaceutical cleaning validation and other related assessments. In this effort, three main topic areas were identified that were in need of harmonization: 1) regulatory guidance and application; 2) operations and process management; and 3) ADE/PDE derivation methodology (Figure 1). However, it should be noted that several individual elements were featured in more than one main topic area of the workshop discussion, underscoring the cross-functional and interdependent nature of ADE/PDE assessment and implementation processes. Each topic area is discussed below.

## REGULATORY GUIDANCE AND APPLICATION

Cross-contamination of pharmaceutical products in shared facilities has been the subject of global regulations and guidances in recent years (ISPE, 2010; EMA, 2014a). The current regulations have evolved over time and reflect differences among regulatory authorities with respect to approaches to cleaning validation. Differences in default

versus chemical-specific risk-based approaches across regulations can be identified by evaluating guidances over time and by organization.

Historically, several default approaches have been used (such as analytical detection levels, visual cleanliness, a predefined fraction of the LD50, or 1/1,000th of the minimum therapeutic dose or LCD) to set ADE/PDEs in pharmaceutical settings, but there was a lack of guidance on how to move away from these defaults (Walsh, 2011a). These guidances also require dedicated facilities for "certain" types of compounds. In more recent years, when data are insufficient to conduct a chemical-specific assessment, alternative science-based approaches have been utilized, including the threshold of toxicological concern (TTC) approach (Dolan et al., 2005).

There are a number of vetted and accepted TTCs available for different toxicological endpoints and specific compounds in the current literature (Kroes et al., 2000; Dolan et al., 2005; Bernauer et al., 2008; Van Ravenzwaay, 2011, 2012; Laufersweiler et al., 2012; Muller et al., 2006; Munro et al., 1996; Stanard et al., 2015).

However, there has been a lag in the regulatory acceptance of the use of these science-based approaches, specifically as it applies to cleaning validation and the cross-contamination of pharmaceutical products. Inconsistent interpretation, lack of clarity, and lack of harmonization also exist among regulatory guidances and can be seen in a simple evaluation of terminology across organizations (ADI, TDI, ADE, PDE, etc.). This confusing landscape of guidances led individual companies to adapt these approaches for their needs and in the process made it more difficult for regulators to use clear acceptance criteria related to pharmaceutical risk assessments. Key conclusions from the workshop included:

## DEFAULT VS. HEALTH-BASED APPROACHES

- Traditional defaults (e.g., 1/1000th clinical dose, 10 ppm, etc.) that take minimal or no account of available data on a compound:
  -Can result in overly stringent limits, or
  -Can result in limits that are not stringent enough.
- Acute oral LD50 testing has not been routinely conducted for many years for APIs or other substances and, in any event, should not be used when other options are available;
- Preference and priority should be given to methods that take into account toxicological or mechanistic data that are available for a compound;
- An appropriate TTC approach provides cautionary guidance that will provide a protective value for most adverse effects and drug classes;
- Occupational exposure bands (OEBs) may be used as a basis for assigning 'health-based' limits for early- to mid-development phase APIs or for prioritization of risk assessments;
- A systematic 'tiered' approach should be considered for selection of approaches when faced with limited data.

## DIFFERENCES IN REGULATORY APPROACHES

- GMP regulations are not globally harmonized and some rely on outdated guidances for cleaning validation;
- Lack of harmonization and lack of clarity in approaches results in inconsistent interpretation and application of GMP requirements by pharmaceutical companies and regulators.

## OPERATIONS AND PROCESS MANAGEMENT

Operations and process management refers to approaches for ensuring that the personnel responsible for developing ADE/PDEs and related product quality acceptance limits (e.g., swab or rinse limits) are qualified to perform this function, as well as addressing approaches for implementing and communicating these limits within and across organizations.

There is a clear need for increased communication (within companies, between companies, and between companies and regulators). Specifically, the sharing of data across companies is critical when contamination arises from the use of shared facilities. While compound-specific operational procedures are available for some classes of compounds in some organizations (e.g., intermediates, degradants, impurities, large molecules, small molecules, etc.), more guidance and harmonization are needed.

A decision process or framework to approach setting ADE/PDEs for different compounds that covers the question of when derivation is or is not necessary would be useful. However, this framework should be flexible enough to conform to individual company management practices, identify robust and transparent documentation of decision points, meet regulatory expectations, and be adaptable to the changing state of the science. Key conclusions from the workshop included:

## OPERATIONAL CONSIDERATIONS

- Apart from the difference in route of exposure, another difference between the ADE/PDE and OEL is the intended target population, (i.e., patient population vs. assumed healthy adult populations in workplaces). However, subtle differences exist among companies in assumptions related to default body weight and adjustment or uncertainty factors that lead to increased variability;
- Converting an OEB or OEL to an ADE/PDE can give a good estimate to determine substances which may pose higher risks for patients and can be used as a priority-setting method together with severity of health hazards;
- There are some important differences that impact the production of small vs. large molecule therapeutics, and also that may impact the production of small molecule API vs. formulated products;
- The availability of documentation for ADEs/PDEs/OELs is critical for several reasons, and it could be beneficial to the industry to establish a minimum description of the data which should be included in this documentation.

## STAKEHOLDER COMMUNICATION

- The basic concept is that the ADE/PDE approach employs a rigorous methodology to accurately determine a safe/acceptable dose for a given substance and a solid implementation plan to ensure the consistent application of practices is employed by cross-functional users in complex organizational systems;
- The ADE/PDE must be technically sound, accounting for and resolving all the data to inform the evaluator or end user, use the most appropriate methodologies, and be scientifically defensible;
- The dataset used to derive the ADE/PDE must be sufficiently robust and any data gaps and resulting potential uncertainties must be appropriately accounted for by other means, such as adjustment factors;
- The methodology used to derive the ADE/PDE must be current, using industry-accepted best practices;

• Documentation of the basis for the ADE/PDE value should be robust, concise, and transparent for the end-user, and should be peer-reviewed for concurrence by an equally qualified individual(s);
• Determination/setting of the ADE/PDE value should be performed by a qualified toxicologist or other equivalent expert with appropriate credentials and experience in this type of assessment and should be reviewed appropriately such that any pertinent new information obtained is incorporated into the value and its justification/documentation on a timely basis.

## ADE/PDE DERIVATION METHODOLOGY

ADE/PDE derivation methodology refers to the actual step-by-step process used by risk assessors to derive safe exposure limits. This generally includes: literature review, selection of key studies, determination of the "critical effect(s)", selection of the PoD, dosimetry and pharmacokinetic (PK) corrections, and application of adjustment factors. The ADE/PDE derivation process also considers the hazard assessment context by incorporating methods specific to toxicological endpoint, route of exposure, and product-specific considerations.

While the dataset for pharmaceuticals varies with the phase of product development, even early-phase development datasets can include studies (e.g., in silico assessments, repeat-dose toxicity studies in more than one species, pharmacology/PK studies, genotoxicity assays, and pharmacodynamic (PD) characterizations) that, with application of appropriate adjustment factors, can inform the derivation of an ADE/PDE value.

The result is a plethora of endpoints for which dose-response data may be available, some of which are common to all toxicity studies (e.g., standard clinical chemistry batteries, organ histopathology, organ weights) and others that are unique for pharmaceuticals such as PD effects and highly sensitive measures of adverse effects. Currently, no harmonized guidance is available that describes when and how to fully leverage the data sets that exist for pharmaceuticals for use in risk assessment.

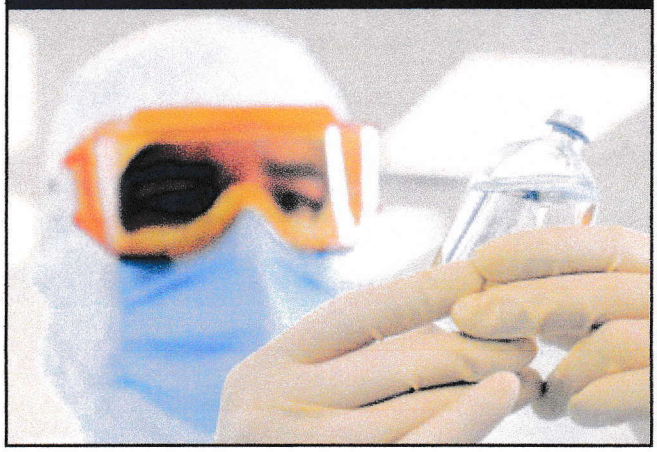
Other areas in need of harmonization include PK adjustments related to dosing intervals, the appropriate human body weight to use for normalization, and route-to-route extrapolation, particularly for non-standard exposure routes (e.g., intrathecal, intraventricular, intravitreal). Although there are a number of papers published on these issues (Pastino et al., 2003; Naumann et al., 2005, 2009; ICH, 2014a; IGHRC, 2006), there is little regulatory consensus or accepted best practices on these issues related to use in the pharmaceutical arena.

Other harmonization needs reflect the use of special toxicological endpoints: cytotoxicity, genotoxicity, reproductive and developmental toxicity, immunogenicity, sensitization, and alternative approaches for different types of pharmaceuticals (e.g., macromolecules/peptides versus small molecules). Finally, a harmonization of adjustment factors to be applied under different data availability scenarios is desired because current guidances are conflicting and generally unclear on this issue. Key conclusions from the workshop included:

## POINT OF DEPARTURE (POD) SELECTION

• The PoD is the starting dose which is used to derive the ADE/PDE;
• Pharmaceuticals represent a unique class of compounds with rich datasets, including studies in humans. Therefore, selection of the PoD should be performed by a qualified toxicologist or other equivalent expert with experience in both pharmaceutical datas-





ets and risk assessment;
• The "critical effect" for a drug can be either pharmacological or toxicological, and clinically significant pharmacological effects are undesired or adverse in the context of an ADE/PDE. This is in contrast to drug development where pharmacology is considered beneficial for the intended patient population;
• The PoD represents a dose for which data show a certain effect level on the "critical effect" considered, optimally the highest dose without a significant effect on the respective parameter;
• The PoD and "critical effect" determine what adjustment factors are needed. For example, for some drugs, such as life-saving anticancer drugs with higher risk tolerance given the benefit provided to the intended patient population, higher adjustment factors may be required to protect all patient populations potentially exposed to the drug as a cross contaminant if the PoD is taken from a therapeutic dose.

## PHARMACOKINETIC ISSUES AND DOSIMETRY

• PK data can be used to support the choice of dose metric and includes free drug/toxicologically active metabolite concentration at the critical receptor site, drug concentrations in the blood, plasma, or other fluids, area under the (time-concentration) curve (AUC), peak plasma concentration (Cmax), clearance rates, glomerular filtration rates, and other measures reflective of the critical target tissue concentration. Selection of the best dose metric is not always clear-cut, and it may not be easy to define the most appropriate one to use;
• Accounting for exposures that are inconsistent with patient dosing, such as less than daily administration or intermittent dosing in toxicity studies, can be done using PK and PD data for duration adjustment of the PoD instead of default time-weighted averaging;
• There are a number of PK and PD considerations for use as chemical-specific data to support replacement of default adjustment factors, including whether the chemical itself or a metabolite is the active species, the relevance of the PK or PD data to the critical endpoint, and how representative the data are of the patient population being protected;
• Several investigations and reviews have provided background on the use of bioavailability correction factors and guidance on when and how they should be applied for ADE/PDE development (many specifically relate to OEL development, but these approaches are relevant to setting ADE/PDEs as well);
• The maximum daily dose [MDD, or maximum recommended human daily dose (MRHDD)] is used to derive product quality limits and is a key component of product carryover and cross-contamination assessments, but there is currently little guidance available on best practices for its use. In relation to PK issues, the lack of guidance for dose-averaging for intermittent dosing schedules is an area of concern related to the MDD.

## ENDPOINT- AND PRODUCT-SPECIFIC CONSIDERATIONS

• Pharmaceuticals can cause a wide-range of toxicity. The approach for risk assessment and determination of the ADE should be adjusted depending on characteristics of the molecule being assessed. One must consider dose-response, pharmacokinetics, physical/chemical properties, and amount of available information on a compound and current techniques to determine safe ADE/PDEs;
• Additional consideration should be given for special endpoints including: cytotoxicity, genotoxicity, reproductive and developmental toxicity, sensitization, immunogenicity, and immunosuppression;
• There are often limited datasets for some APIs and synthetic intermediates; however, approaches exist to assess the hazards and manage risks in the absence of critical data;
• Product-specific considerations are used to evaluate special molecules such as: antibody drug conjugates (ADCs), large molecules/peptides vs. small molecules, and solvents and metals versus other impurities.

## ADJUSTMENT FACTORS

• Depending on the PoD used, adjustment factors for interspecies extrapolation, inter-individual variability, exposure duration, and extrapolation to a NOAEL or No-Observed-Effect Level (NOEL) may be applied. Further factors (e.g., for severe toxicity or database completeness) may be applied on a case-by-case basis;
• Although organizations may use slightly different adjustment (safety/uncertainty) factors, the overall uncertainty and need for other adjustments are generally accounted for;
• Although adjustment factors should be considered individually, it should be noted that they are not independent of each other.

## CONCLUSIONS AND NEXT STEPS

A harmonized core set of recognized scientific principles is needed to inform individual efforts in calculating, interpreting, and implementing pharmaceutical risk assessments. Ultimately, this harmonization effort should foster closer alignment of methods among risk assessors and increase the ability of outside parties, including regulatory bodies and project managers, to understand and accept the ADE/PDE values derived.

Detailed outcomes and conclusions for each workshop topic will be published as a series of publically accessible reports. It is hoped that these reports will shed light on inconsistencies and data needs, lead to further research of the knowledge gaps, and contribute to informing decision making among risk assessors in the pharmaceutical industry by providing a "guide to best practices" that further the value of and builds on current international guidelines.

It is also hoped that this effort will serve to stimulate discussion among industry partners and government agencies, so that the interests of all parties in achieving practical, science-based, and health-protective exposure limits can be best served. **CP**

**For a list of references please visit the online version of this article at contractpharma.com.*

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