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A harmonization effort for acceptable daily exposure derivation – Considerations for application of adjustment factors

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ABSTRACT

Acceptable daily exposures (ADEs) are established to determine the quantity of one drug substance that can contaminate another drug product without causing harm to the patient. An important part in setting an ADE for a drug substance, after identification of the unwanted critical effect(s) of the compound (see Bercu et al., 2016, this issue), is the determination of an appropriate overall margin of safety that is need to be maintained below the dose causing a certain critical effect (*i.e.*, the point of departure or PoD). The overall margin of safety used to protect the general patient population from critical effects is derived as the product (*i.e.*, composite adjustment factor) of various individual factors that account for variability and uncertainty in extrapolating from the PoD to an ADE. These factors address the considerations of interindividual variability, interspecies extrapolation, LOAEL-to-NOAEL extrapolation, exposure duration adjustment, effect severity, and database completeness. The factors are considered individually, but are not necessarily independent and their interdependence should be identified, with subsequent adjustment to the composite factor, as appropriate. It is important to identify all sources of variability and uncertainty pertinent to the derivation of the ADE and ensure each is considered in the assessment, at least by one of the adjustment factors. This manuscript highlights the basis for and selection of factors that address variability and uncertainty as used in the guidance documents on setting ADEs or other related health-based limits.

1. Introduction

An acceptable daily exposure (ADE) value represents the quantity of a contaminant that can exist in a drug product that would not be expected to cause adverse effects in patients receiving that drug, by any route, even if exposed for a lifetime (ISPE, 2010). The goal of quantitative risk assessments, including the important first step of setting ADE values, is consistent with the basic principle of toxicology: "The Dose Makes the Poison". The process involves developing a value that will, in Paracelsus' words, "differentiate a poison from a remedy". However, an active pharmaceutical ingredient (API) or other potential cross-contaminant would have no benefit to the patient and the ADE would be derived to limit contaminant exposure to a dose that has no adverse health effects. Once the critical endpoint(s) and points-of-departure (PoD) have been identified (Bercu et al., 2016, this issue), an appropriate overall "Margin of Safety" should be achieved which prevents effects from occurring in the population targeted by the risk assessment. PoDs can include (but are not limited to) no-observed-(adverse)-effect-levels [NO(A)EL], lowest-observed-(adverse)-effect-levels [LO(A)EL], and benchmark doses (BMD) (Bercu et al., 2016, this issue). The overall composite adjustment factor contributes to the overall margin of safety and represents the product of several separate factors that account for variability and uncertainty in the PoD as it compares to the target population (*e.g.*, extrapolation from animal to human, interindividual variability, *etc.*). The factors accounting

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for variability and uncertainty have historically been labelled as "safety" or "uncertainty" factors depending on the regulatory jurisdiction. However, the term "adjustment" factor (AF) will be used in this manuscript to cover both variability (due to heterogeneity or diversity) and uncertainty (due to a lack of information) (US EPA, 2002). Other adjustments can also be applied to the PoD such as pharmacokinetic/toxicokinetic adjustment for route-to-route extrapolation (bioavailability correction factors), achieving steady-state, *etc*. (Reichard et al., 2016, this issue). Both the terms pharmacokinetic (PK) and toxicokinetic (TK) [along with pharmacodynamic (PD) and toxicodynamic (TD)] are used in this paper. In the practice of toxicology and risk assessment, the terms TK and TD are often used in preference to the terms PK and PD. In general, PK and PD are used in relation to therapeutic doses of pharmaceuticals where the intent is to provide a link between preclinical studies and humans, or to characterize or tailor the therapeutic use of pharmaceuticals. In contrast, TK and TD are more recent extensions of the PK and PD concepts that describe adverse effects occurring at supra-therapeutic doses, and carry the connotation of harm rather than therapeutic benefit (Welling, 1995). Both terms are used interchangeably throughout this document depending on the context and source of the information.

Establishing occupational exposure limits (OELs) for worker safety in pharmaceutical manufacturing is a practice that has been employed successfully for many years (Sargent and Kirk, 1988). Establishing ADEs for patient safety uses similar methods, and thus, in some cases an existing OEL derivation has been used to support the ADE development process. While leveraging data can be useful, caution is also needed since ADEs are derived for a specific purpose that is different than that of an OEL. When selecting adjustment factors for calculating ADEs for use in any risk assessment, it is essential to identify the target population of the assessment and determine whether any susceptible subpopulations may exist. For example, the target populations for ADEs may be different from those for OELs, which are primarily healthy working adults. Sensitive subpopulations of significant size may also exist in the workplace (women of childbearing potential, asthmatics, *etc*.). However, including children, the elderly, or gravely ill individuals in the derivation of an exposure limit may not be appropriate in OEL scenarios. When calculating ADEs, however, these subpopulations and others may need to be considered as these values are generally applied to whole populations using pharmaceutical products. Other differences between OELs and ADEs include route of exposure and duration of exposure. Therefore, it is possible that adjustment factors used for an ADE derivation may be different than for an OEL. As a result of these differences, OELs should only be used as a screening tool to estimate ADEs to identify the highest risk products and with the assistance of a qualified toxicologist or other expert (Faria et al., 2016, this issue). However, the basis for the derivation of OELs and ADEs is similar in that they typically both have the same underlying database, use many of the same scientific principles, and advancements made in OEL or ADE derivations are typically applicable to both types of limits.

Sources of variability, uncertainty, and additional adjustments that are typically addressed in quantitative risk assessment include, but are not limited to:

- Interindividual variability (*i.e*., variability in human susceptibility);
- Interspecies extrapolation (*i.e*., differences in sensitivity between animals and humans);
- LOAEL-to-NOAEL extrapolation;
- Exposure length adjustment factors;
- Severity of effect; and
- Database completeness.

Additional adjustment factors can also be considered that relate to adjusting the dose from the regimen in the study that provided the point of departure (PoD) to the exposure scenario being addressed in the assessment. Two such considerations often address bioavailability (route-to-route extrapolation) and bioaccumulation (steady-state adjustment). The basis of these dose adjustment factors, as well as more details on the use of toxicokinetic and toxicodynamic data is provided by Reichard et al. (2016, this issue).

Each of these sources of variability and uncertainty should be considered critically when deriving an ADE. It is important to identify all sources of uncertainty and variability and make sure all are covered, at least by one of the adjustment factors. Most methods, published or promulgated, consider all these sources, but do not necessarily enumerate them specifically or in the same set of individual factors. While implementation of adjustment factors in risk assessment is common practice across most areas of health risk assessment, the methods can differ significantly with respect to suggested default values, weight of evidence and mode of action considerations for selection, how to move away from and justify not using default values, and the level and detail of the documentation in the decisions made during adjustment factor selection. In addition, whereas each of these factors might be considered individually, it should be noted that they are not necessarily independent and a potential exists for overlap in the factors resulting in the possibility of a larger than needed composite adjustment factors than would be required by the dataset as a whole. Where possible, the interdependent factors should be identified and adjusted, as appropriate. Scientific judgment is needed to understand the interdependence of these factors, where some overlap exists, and to quantify the overall composite adjustment factor necessary for a given compound. Ultimately, application of adjustment factors is a scientific judgment decision made based on science and risk policy, and so some variation in final AF values and the resulting ADEs is to be expected. However, application of a systematic approach is intended to reduce this variation and improve understanding on the basis for differences in ADE derivation (Dankovic et al., 2015). This manuscript highlights the adjustment factors used in the EMA guideline on setting health-based limits (EMA, 2014) and Risk-MaPP (ISPE, 2010) (along with other relevant guidance documents). For each of the main factors discussion includes issues and considerations for increased harmonization.

2. Interindividual variability

The adjustment factor that addresses interindividual variability (AF_H) (also referred to as intraspecies or human-to-human variability) accounts for toxicokinetic (TK) and toxicodynamic (TD) variations within the human population and is intended to protect sensitive subpopulations that may be more susceptible due to their age, sex, genetics, pre-existing diseases, *etc*., compared to the study population used to determine the "critical effect". The EMA guideline recommends the adjustment factor F2 "to account for variability between individuals". Risk-MaPP recommends use of the term UF_H for this purpose, so the two documents are aligned with respect to application of this adjustment factor.

A default factor of 10 is typically used for AF_H (EMA, 2014; ISPE, 2010). A key consideration for setting an appropriate AF_H is the likelihood and severity of effects that might occur in sensitive subpopulations that may be uniquely susceptible to a trace contaminant in another drug. For example, in the case of approved drugs, the product labeling (*e.g*., package insert) identifies subpopulations (*e.g*., gender, ethnicity, age) and whether or not group-specific dosage adjustments are needed. Sensitive subpopulations may also be identified by looking at the mechanism of action (*e.g*.,