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Point of departure (PoD) selection for the derivation of acceptable daily exposures (ADEs) for active pharmaceutical ingredients (APIs)

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ABSTRACT

The Acceptable Daily Exposure (ADE) derived for pharmaceutical manufacturing is a health-based limit used to ensure that medicines produced in multi-product facilities are safe and are used to validate quality processes. Core to ADE derivation is selecting appropriate point(s) of departure (PoD), *i.e.*, the starting dose of a given dataset that is used in the calculation of the ADE. Selecting the PoD involves (1) data collection and hazard characterization, (2) identification of "critical effects", and (3) a dose-response assessment including the determination of the no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-level (LOAEL), or calculating a benchmark dose (BMD) level. Compared to other classes of chemicals, active pharmaceutical ingredients (APIs) are well-characterized and have unique, rich datasets that must be considered when selecting the PoD. Dataset considerations for an API include therapeutic/pharmacological effects, particularities of APIs for different indications and routes of administration, data gaps during drug development, and sensitive subpopulations. Thus, the PoD analysis must be performed by a qualified toxicologist or other expert who also understands the complexities of pharmaceutical datasets. In addition, as the pharmaceutical industry continues to evolve new therapeutic principles, the science behind PoD selection must also evolve to ensure state-of-the-science practices and resulting ADEs.

1. Introduction

Product quality is imperative to the manufacture of pharmaceuticals (also called drug products or medicinal products). Product quality comprises many aspects, including identity, purity, and stability of the product, uniformity of dosing units, and minimization of chemical contamination. Therefore, quality risk management principles are applied to all manufacturing steps such as synthesis, pharmaceutical production, packaging, labeling, and storage. The basics for this process are outlined by the International Conference on Harmonization (ICH) in the Q9 Guideline on Quality Risk Management (ICH, 2005).

One aspect that demands particular attention when drug products are produced in multi-product (shared) facilities is the potential cross-contamination of the drug product with other drug products handled in the facility (Olson et al., 2016, this issue). While a drug product provides a benefit to the intended patient, as a potential cross-contaminant it would provide no benefit to the unintended patient and may even pose a risk. Hence, the presence of such potential cross-contamination has to be restricted to a level that can be considered not to present a relevant risk to the patient.

In recent years the use of substance-specific health-based limits has been promoted as a tool to manage potential risks related to cross-contamination of drug products. The fundamental part of the health-based limit is the derivation of the Acceptable Daily Exposure (ADE), which has been alternatively referred to as the effectively synonymous term Permitted Daily Exposure (PDE). The ADE is defined as a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime (Olson et al., 2016, this issue). It is derived from a thorough evaluation of available toxicological and pharmacological data of the substance, including data from animal experiments as

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well as human/clinical data (EMA, 2014; ISPE, 2010).

The establishment of an ADE is a complex process that requires expertise in pharmacology and toxicology as well as the principles of risk assessment and health-based limit setting. It principally involves the following steps:

I. hazard identification by reviewing all relevant data,
II. identification of the "critical effect(s)",
III a dose-response assessment of the critical effects and determination of the point of departure (PoD) as the starting dose for the calculation of an ADE, *e.g.,* a no-observed-(adverse)-effect level [NO(A)EL], lowest-observed-adverse-effect-level [LO(A)EL], or modeled estimate such as benchmark dose (BMD) for each critical effect, and
IV calculation of the ADE by applying adjustment factors (AFs) to account for various sources of variability and uncertainty when extrapolating from the PoD, as well as differences in pharmacokinetics when extrapolating from different dosing patterns and routes of exposure (Reichard et al., 2016; Sussman et al., 2016; both this issue).

The aim of this manuscript is to describe in more detail the first three steps of this process, with particular focus on the selection of appropriate PoDs. Specific considerations for setting an ADE for active pharmaceutical ingredients (APIs) are discussed.

2. ADE calculation

General formulas for calculating ADEs have been published in the different guidelines that vary slightly st first read, but generally follow the same principle (Equation (1)):

$$ADE = \frac{PoD \times Body\ Weight\ Adjusment}{AF1 \times AF2 \times \ldots AFX \times PK} \quad (1)$$

where AFs are the adjustment factors for different areas of uncertainty (Sussman et al., 2016, this issue) and PK is the pharmacokinetic adjustment factor that accounts for dosing route and duration considerations (Reichard et al., 2016, this issue).

The PoD is the starting dose for the calculation of an ADE. It is noteworthy that not all current pharmaceutical risk assessment guidelines use the term "point of departure" explicitly; some only refer to identification of a certain effect level, *e.g.,* no-observed-effect-level (NOEL) (ICH, 2011) or NOAEL (EMA, 2014). However, the concept is embedded in all the key guidance documents pertinent to ADEs. In risk assessment applications, PoD can be defined as "The dose-response point that marks the starting point for low-dose extrapolation" (US EPA, 2012). It represents a dose for which experimental data (*i.e.,* from nonclinical studies) or human data show a certain response level for the critical effect considered. In practice, the PoD can be a NOEL, NOAEL, lowest-observed-effect-level (LOEL), LOAEL, or a modeled estimate such as a BMD or its lower bound estimate (BMDL) (Crump, 1984). For a pharmacological or toxicological effect of a substance that has a sigmoidal dose-response relationship (Fig. 1), the NOAEL would be the highest dose that did not increase the incidence of the relevant adverse effect being studied and the LOAEL would be the next higher dose. Alternative PoDs can include modeled BMD values. Optimally, the dose selected as the PoD represents the best estimate of the boundary of the onset of adverse effects, and is typically selected as the most relevant NOAEL where a modeled estimate (BMD) is not available.

The ADE is typically presented in units of mg/day. As a result, the PoD, when derived from a pharmacology or toxicology study, may need to be converted to mass/day units. The body weight

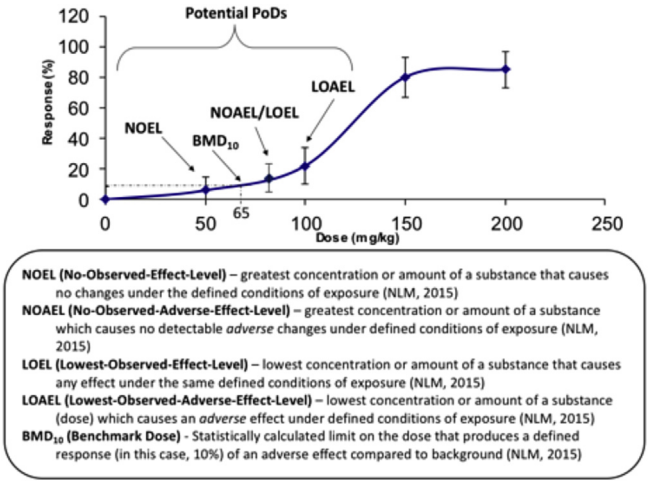

Fig. 1. Pictorial representation of the dose-response curve used to derive the PoD for an identified critical effect.

adjustment applied is dependent on the unit in which the study PoD is given, which may either be on a mg/day basis or on a mg/kg-day basis. The PoD from animal studies is typically in units of mg/kg-day, while the clinical studies can be reported as mg/day per patient, mg/surface area (m^2), or mg/kg-day. To convert from one set of units to another, a body weight of 50–60 kg (EMA, 2014; ICH, 2011; ISPE, 2010; US FDA, 2005) and body surface area of 37 kg/m^2 (US FDA, 2005) can be assumed. The body weight value used depends on the regulatory domain being addressed and the characteristics of the population to which the ADE will be applied. In most cases, there is no clear scientific rationale for the default body weight choice, however, it is important to have a clear policy and apply it consistently. For example, the ICH Q3C notes that a 50 kg body weight is used and provides an additional safety factor compared to the 60 kg or 70 kg values used by other organizations (ICH, 2011). If the ADE is developed for pediatrics, a body weight of 11.4 kg (based on a 25-pound child – 16 CFR 1700.12) or 20 kg (US FDA, 2005) can be assumed (Hayes et al., 2016, this issue).

AFs are then applied to the body weight-adjusted PoD. AFs are specific to the PoD selected and account for various sources of variability and uncertainty in the available dataset, including interspecies extrapolation, inter-individual variability, exposure duration, and extrapolation from a measured LOAEL to an estimated NOAEL if applicable. Additional AFs (*e.g.,* for severe toxicity or lack of database completeness) may be applied on a case-by-case basis (for more details on AF selection and application, see Sussman et al., 2016, this issue).

Pharmacokinetic (PK) AFs may be applied to account for differences in bioavailability when extrapolating between different routes of exposure, or where needed, to account for potential bioaccumulation due to a long half-life and when extrapolating from a discontinuous dosing regimen to a daily or multiple-dose scenario (for more details on PK adjustments, see Reichard et al., 2016, this issue).

Principally, the ADE may be defined as a dose that is safe by all routes of administration, including dermal, oral, parenteral, inhalation, and intrathecal. When developing an ADE, the most protective route may be used to apply to all other routes. An ADE may also be derived for a specific route and in this case the PoD should be selected based on the data for the most relevant route of exposure to the risk assessment scenario being evaluated. In many cases, however, these route-specific data are not available and therefore appropriate PK adjustments are applied. Additional