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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.

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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

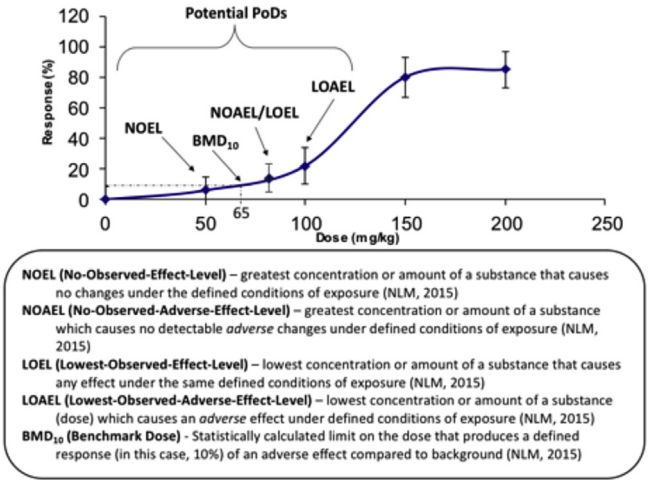


Fig. 1. Pictorial representation of the dose-response curve used to derive the PoD for an identified critical effect.

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

consideration may be given to possible local effects of a substance by a specific route of administration. An alternative approach outlined by some guidelines (ICH, 2014a) and applied by companies is to derive route-specific ADEs, *e.g.,* oral, parenteral, and inhalation (Olson et al., 2016, this issue). Some companies derive a single ADE for the worst-case route of exposure.

3. Types of available data for hazard characterization

An initial step in the derivation of an ADE is a detailed data collection process for the substance of interest. A full, systematic literature review, which aims to identify all high quality data available relevant to ADE derivation, is important and necessary in this process and improves the hazard characterization. Optimized search strategies should be used to find these data and internal strategies can be implemented to ensure that all relevant databases and sources of information have been queried for the compound of interest (Sandhu et al., 2014). This approach also provides documentation of the search such that it can be repeated by others. Currently, there is no guidance from any of the regulatory agencies on how to do systematic review effectively, although general guidelines on the principal are available (EFSA, 2009; Rhomberg et al., 2013).

Literature searching should be performed or reviewed by a toxicologist or other qualified risk assessment expert. While development of a systematic review strategy is a useful guide, literature searching can also be an "art" that is efficiently performed by an expert who can effectively identify alternative data streams based on initial search results. In practicality, there are data-rich compounds and data-poor compounds and no search is identical. Each compound or set of compounds has complexities in the literature search process. The data-rich compound can have hundreds of references with data that repeat in various references or is not relevant to ADE derivation. In such cases, only a few key, relevant references are typically used to set an ADE. The data-poor compound can have very few references and the literature must be thoroughly mined to find the few key sources of information that will impact the setting of a health-based limit. An expert can efficiently determine the literature search strategy based on the type of compound (data-rich or data-poor). The permutations of search strategies are too numerous to describe in this manuscript, but in general it is good to take an iterative approach by first searching databases that generate the most data to cast a wide net, and focusing on the more specialized databases depending on the results of the first search. There may be instances where data are only available to the innovator company, which may result in gaps of data for non-innovator companies. An expert can determine where the data-gaps occur, and may either try to obtain the data, fill in the gaps as best as possible (*e.g.,* read across, mechanism, *etc.*), use defaults such as the Threshold of Toxicological Concern (TTC), or apply a larger adjustment factor due to increased uncertainty from lack of data. Additional data (outside of proprietary data) can be used in the weight of evidence (WOE) assessment, in the mode of action (MOA) evaluation for ADE derivation, and for read-across to fill in data gaps for compounds with a comparable MOA. Typical sources of data include:

- Publically available information such as peer-reviewed journal articles and pharmacopeias,
- Regulatory information, including prescribing information and information provided by regulatory bodies such as the FDA's Summary Basis of Approval (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, US FDA, 2012), or EMA's European Public Assessment Report (EMA, 2015), and
- Proprietary data, internal to the innovator company, such as the Investigator's Brochure or study reports.

The hazard characterization process includes a potency and pharmacological/toxicological evaluation of the available dataset. The ultimate deliverable from the systematic review includes: identification of a series of endpoints relevant to the assessment being conducted with all potential PoDs identified; and characterization of key data gaps. The robustness of the dataset available for review will vary from API to API, as will the necessary depth of review. Sources of data will vary depending on whether the assessor has access to proprietary data for an API. While not an exhaustive list, the following endpoints are typically available for review on a commercial-stage API:

- Pharmacological nonclinical data – dose or mechanistic information for the desired clinical response for the API,
- Toxicological nonclinical data – safety information used to identify the hazards or undesired effects of the API, and
- Human data – clinical data, which includes data both in volunteers and patients which are used to determine the clinical pharmacodynamics, pharmacokinetics, safety, and efficacy of an API.

3.1. Pharmacological nonclinical data

The main difference between drug therapeutics and chemicals such as solvents and synthesis impurities is that APIs have desired, deliberate, and well-characterized (studied) pharmacological effects. Therefore, during data collection, factors related to the mechanism of action such as target receptors, potency, pharmacological effect(s), and the indication(s) for the drug product are of importance.

Relevant nonclinical pharmacological data may include:

- Experimental data from *in vitro* studies on the pharmacological target of the API [*e.g.,* half maximal inhibitory concentration (IC_{50}) and/or inhibition constant (K_i) values] as well as off-target effects (*e.g.,* effects on other enzymes and receptors),
- Data from nonclinical experiments including dose-response relationships, *e.g.,* those related to activity in disease-related animal models, and
- Data on safety pharmacology parameters, such as on central nervous system, cardiovascular, and respiratory function.

3.2. Toxicological nonclinical data

All available and relevant toxicological data of the substance should be compiled and considered. This primarily includes data from animal experiments, such as:

- Single dose toxicity studies,
- Repeat dose toxicity studies,
- Developmental and reproductive toxicity studies,
- Genotoxicity and carcinogenicity studies, and
- Other toxicity data of particular interest (*e.g.,* local tolerance, immunotoxicity).

The toxicology data should identify the critical effect(s) and the dose-response relationships of the observed effects. Toxicology studies will also provide data on internal doses based on pharmacokinetics of the substance. Of particular relevance are the maximum plasma levels (C_{max}) and area under the curve (AUC)

values at the tested dose levels. For more details on how to use kinetic parameters in the risk assessment see Reichard et al. (2016, this issue).

3.3. Human data

Pharmaceuticals are unique from other classes of chemicals in that the inherent properties are extensively studied and characterized in humans (*e.g.,* healthy volunteers, clinical subjects, patients). One major difference for APIs compared to other chemicals is that during the development of an API, and also after submission, human data are generated. Where available, these human data are often of higher relevance than animal data for the same endpoints, for example regarding the pharmacological effects and adverse clinical effects. When not yet available, as with early-stage APIs, human kinetics and projected therapeutic doses may be estimated based on available nonclinical data.

Characteristics of a robust clinical dataset for an API could include:

- Information on pharmacological effects and its dose-dependency, the indication, and range of therapeutic doses (including for sensitive subpopulations),
- Adverse effects observed at therapeutic doses, and optimally also the dose-dependency of these effects, including adverse effects at sub- and supra-therapeutic doses,
- Pharmacokinetics in humans including all available absorption, distribution, metabolism, and excretion (ADME) parameters in healthy and patient populations,
- Information on effects and precautions/contraindications for specific subpopulations, such as patients with severe renal or liver impairment, or pregnant women, and
- Interactions of the API with other pharmaceuticals.

4. Identification of “critical” effect(s)

The “critical effect” has been defined as the “most sensitive adverse effect that is considered relevant to humans” (Naumann and Sargent, 1997) or the “first clinically significant adverse effect that is observed as the dose increases” (ISPE, 2010). For an API with a favorable therapeutic index, the critical effect is often identified as the intended pharmacological activity. This follows the assumption that all effects, both intended pharmacology and unintended toxicity, are considered adverse in a potential cross-contamination scenario. There may also be adverse effects occurring at higher doses, but that may need higher AFs applied, based on a limitation in data (*e.g.,* only animal data for the particular endpoint), the severity of effects (*e.g.,* severe organ toxicity, developmental toxicity, carcinogenicity), or the values of internal dose metrics (Sussman et al., 2016, this issue). Thus in many cases, and depending on the effects observed (*e.g.,* pharmacological, organ toxicity, reproductive/developmental toxicity), more than one candidate critical effect may be identified for PoD selection in the derivation of the ADE. For each such candidate critical effect identified, consideration should be given to the dose-response relationship of the effects; including plasma levels at which these effects are occurring, the severity of the effects, and the frequency of occurrence and reversibility of the effects. Formal weight of evidence techniques can also assist in this process (Rhomberg et al., 2013).

An ADE may be calculated for each of the candidate critical effects. This is recommended because each identified critical effect will generally necessitate different AFs, meaning that the effect occurring at the lowest dose identified might not always correspond to the lowest ADE derived. In general, the lowest of these derived values is selected as the final ADE if it is considered relevant for the target population. While clinical pharmacology data serve as the most sensitive endpoint in most cases, toxicological findings can also yield the lowest ADE. This is most common for toxicology endpoints that generally cannot be (sufficiently) monitored in humans, but are particularly critical. These include genotoxicity, carcinogenicity, and reproductive and developmental toxicity. In some cases, nonclinical toxicology data might yield a lower ADE, but still not be selected as the final value. Examples of this are an effect that is not considered to be of relevance for humans, or an effect that is observed in both humans and animals. When an effect is observed in both animals and humans, it is common for the animal-based ADE to be lower since AFs using animal data are typically higher given the uncertainty in extrapolation between species. However, the human data are more relevant with reduced uncertainty and should be used, despite the higher ADE.

5. Selection of the PoD

The PoD can be an effect level from a study or a modeled estimate of the dose-response from animal or clinical data. In most guidance documents relevant to ADE (and related assessments) the use of a NOEL or NOAEL, or a modeled surrogate of this value, is specifically mentioned as the preferred PoD basis. The traditional definition of the NOAEL has been mainly used for the purposes of animal toxicity. Adversity has been defined as “A biochemical, morphological or physiological change (in response to a stimulus) that either singly or in combination adversely affects the performance of the whole organism or reduces the organism's ability to respond to an additional environmental challenge” (Lewis et al., 2002). Adverse effects that are biologically significant, even if not statistically significant, should be considered in determining a NOAEL (US FDA, 2005). Adversity is further defined by Dorato and Engelhardt (2005) in the context of drug development as “toxicologically relevant increases in the frequency or severity of effects between exposed and control groups based on careful biological and statistical analysis. While minimum toxic effects or pharmacodynamic (PD) responses may be observed at this dose, they are not considered to endanger human health or as precursors to serious events with continued duration of exposure.”

It should be cautioned that in the context of selecting the PoD for an ADE calculation, the NOAEL in nonclinical studies can be different than the NOAEL in clinical studies. The goal of drug development is to determine the therapeutic window, which is the margin of safety (MOS) of the NOAEL observed in animals over the effective dose in the clinic. Some effects observed in toxicology studies are not reported to be adverse if they are an extension of the intended pharmacologic effect of the drug. However, the patient taking a medicine intentionally for a specific indication receives a benefit from the medicine at the effective dose. In contrast, an unintended exposure - as a potential trace contaminant in another drug - to an effective dose is considered adverse. Therefore, the definition of a NOAEL when used to derive an ADE is a dose at which there is no biochemical, morphological, or physiological change (in response to a stimulus) that either singly or in combination adversely affects the performance of the whole organism or reduces the organism's ability to respond to an additional environmental challenge. In addition, it is a dose at which there is no “clinically relevant” pharmacological response when consumed by a different patient population. Although some guidance documents denote the NOEL as the PoD, it is noteworthy that the intent is to protect from adverse effects as described in this section and the concept of NOAEL applies regardless of guidance nomenclature.

Ideally the NOAEL from the dose-response should be selected as the PoD for a specific critical effect. When not available, the LOAEL

should be used. In contrast to the NOAEL, the LOAEL is an adverse dose, ideally close to the threshold and typically the lowest observed dose causing statistically and toxicologically significant responses as compared to control. In some cases, only a frank effect level (FEL, *i.e.,* an exposure level which produces unmistakable adverse effects, such as irreversible functional impairment or death) is available for a specific endpoint. In these cases, a decision is needed on whether the respective study data are adequate to be used for PoD selection or whether better data are available (or are needed). If no other relevant data on the respective endpoint are available, the nature and severity of effects have to be taken into account as well as the shape of the dose-response curve when choosing the AF for the extrapolation from a LOAEL or FEL to an estimated NOAEL. Additionally, a modifying factor or AF for severity of effect may be needed (see Sussman et al., 2016, this issue).

The BMD approach is an accepted practice in lieu of the NOAEL (EMA, 2014). The value typically applied is the BMDL, which is defined as "a statistical lower confidence limit to a dose producing some predetermined increase in response rate such as 0.01 or 0.1" (Crump, 1984). The BMD approach is recognized as an accepted practice in most cases and in many risk assessment sectors, and it has been recognized that this approach provides advantages to the NOAEL approach, including providing an estimate of the PoD that is independent of study design, taking into account the dose-response curvature in the estimate, and ability to report statistical confidence in the estimate (Travis et al., 2005). BMD modeling has had limited application in pharmaceutical risk assessment perhaps due to concern over regulatory acceptance or internal company procedures, although it is a recommended option to define the PoD by the Veterinary International Conference on Harmonization (VICH, 2015) (at least for use in residues of veterinary drugs in human food), EMA (2014, as an alternative to the NOAEL), US EPA (2012), EFSA (2009), IPCS (2005), and other regulatory agencies across multiple risk assessment sectors. For the calculation of the BMD, a specific software package was made available from the US EPA (2012). Despite the lack of common use of BMD in lieu of API NOAELs, the concept of using modeling of dose-response behavior to establish effect levels is not uncommon for APIs. Pharmacodynamic modeling to estimate efficacious doses is often done as part of clinical study design and such modeling outputs can also serve as the basis for a PoD. In using such estimates, having information on the highest non-efficacious dose is particularly useful. When available, decisions regarding the amount of pharmacological activity that most closely corresponds to a NOAEL versus a LOAEL should be made.

5.1. PoD selection for APIs

For APIs, the datasets are typically robust and there are a number of critical effects and datasets available for use in PoD selection. For each potential PoD, there are a number of considerations that must be addressed, such as species relevance of effect, target population and risk/benefit assessment, local versus systemic effects, datasets indicative of alternative approaches (such as TTC), and others. These are discussed in detail below.

5.1.1. Therapeutic, sub-therapeutic, and pharmacodynamic (PD) effects

The therapeutic dose can be an acceptable PoD for ADE extrapolation for certain drugs for which adverse events from pharmaceutical administration are mild and/or there are no specifically excluded subpopulations due to toxicity concerns. The therapeutic dose is the dose at which patients receive a beneficial effect such as treatment for a disease. There are risks associated with the use of pharmaceuticals that prescribed patients are willing to accept for the benefit of the drug. Certain drugs have higher risks but the benefit is greater, such as life-saving cancer medications. In some of these cases, the therapeutic dose is higher than the dose that causes toxic effects observed in animals (ICH, 2009). In some cases, the drug is restricted in certain patient populations. A common example is that a many drugs are contraindicated in pregnant women. Thus, the therapeutic dose can be an acceptable PoD in many instances but careful review of the indication and patient population is necessary to determine if its use is appropriate for ADE derivation. When relying on clinical dosing information as the PoD, the lowest recommended therapeutic dose in the most sensitive subpopulation is often used as PoD.

The typical dosing schedule for a pharmaceutical should be considered during ADE extrapolation. For APIs with >1 daily dose [*e.g.,* twice-daily divided dose (BID)]: as the ADE is expressed as a daily dose, generally the total daily human therapeutic dose is used. But also acute effects of a single dose have to be taken into account, as a single dose may have a clinically relevant effect. For APIs with <1 daily doses, *e.g.,* for dosing schedules such as once weekly or monthly, generally PoD as a prorated daily dose can be used, *i.e.,* the single dose divided by the number of days between dosing. However, pharmacokinetics (PK) or pharmacodynamics (PD) can be used to derive the daily dose as well (see Reichard et al., 2016, this issue). For example, the elimination rate may not remain first order over the dosing range such that accumulation is not expected at lower doses. If only single or intermittent dose data are available, the accumulation ratio can be used in the calculation of the daily dose (Reichard et al., 2016, this issue; Rowland and Tozer, 1980).

While the therapeutic dose may be a suitable PoD in certain cases, the PoD from PD data may offer better precision. There are two types of PD data available for pharmaceuticals. The first type of PD data is from nonclinical studies. These studies are used to build a PK/PD model and predict a potentially efficacious dose in humans. These data and the resulting PK/PD model are useful for early-phase pharmaceuticals or for pharmaceuticals where no PD studies are conducted in humans. In some cases, the minimal-anticipated-biological-effect-level (MABEL) is identified from the PK/PD model (EMA, 2007) or a no-anticipated-biological-effect level can be extrapolated from the PK/PD model. The second type of PD data is from clinical trials. These studies are typically performed in a limited number of human volunteers and range of doses. Biomarkers are often measured to determine the physiological effect. During the PD study, there is dose-escalation and a target. The results of the Phase 1 study help guide patient studies in Phase 2 and 3, which require a longer duration and more subjects who are patients. While less comprehensive than Phase 2 and 3 data, Phase 1 PD data are valuable for PoD selection as sub-therapeutic doses are tested and sensitive biomarkers are measured. A dose level showing no "clinically relevant" changes could be used as the PoD. When deriving an ADE from PD effects the AFs are typically lower than when the calculation is based on the therapeutic dose or on adverse effects.

An example of the utility of PD studies for PoD selection was demonstrated using dapagliflozin by Gould et al. (2013). Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (E.R. Squibb & Sons, L.L.C., 2014). In a Phase 1 study, 36 healthy volunteers were dosed 0.001–2.5 mg/day where the PD parameter measured was urine glucose concentration 24 h post-dose using a urine glucose dipstick. A significant increase in urine glucose excretion, which was considered an adverse effect and the critical effect, was observed at doses of 0.3 mg/day and above but not at 0.1 mg/day and below. A dose of 0.1 mg/day was determined to be the NOAEL and the resulting PoD.

The article by Gould et al. (2013) provided some key learnings for using PD data as the PoD. First, PD responses can be observed significantly below the therapeutic dose and in this case were 50-fold less than the therapeutic dose. Second, it leads to the measurement of more sensitive effects, thereby reducing uncertainty in the ADE assessment. Knowing that the PoD is 50-fold less than the therapeutic dose and no effect was observed in humans, the authors applied a total AF of 1 to the PoD. By reducing uncertainty, the need for a traditional AF is obviated and the PoD that is selected is closer to the ADE versus requiring large AF. This is consistent with EMA guidance (EMA, 2014) which states that the traditional PDE calculation (PDE used in guidance document) may be inappropriate when using human data. Moreover, traditional risk assessment methods (*e.g.,* US EPA RfD derivation) include examples of low AF application if the PoD is based directly on the no effect dose for a sensitive population.

However, in this context, the relevance of the identified effects on a specific biomarker has to be taken into account. A typical very sensitive biomarker in a clinical study may for example be the enzyme/receptor inhibition at the pharmacological target of the compound. Effects on enzyme/receptor inhibition are typically dose-dependent and a no effect level for such an effect may be very low, while any relevant effects on clinical parameters may only occur with a substantial degree (*e.g.,* > 80–90%) of target inhibition. Another example would be minor changes in gene expression levels in a genomic study. For the selection of the PoD, expert judgment on the relevance of the respective biomarker is needed, whereby the changes in clinical parameters/normal physiological function are of higher relevance compared to an effect such as enzyme inhibition or gene expression without change in physiological function. Just as for setting ADEs, the consideration of early effect biomarkers as inputs to the PoD selection process is gaining additional attention for setting health-based limits in environmental and occupational risk assessments (reviewed in DeBord et al., 2015; Meek and Lipscomb, 2015).

5.1.2. Genotoxicity as a PoD in ADE development

Available genotoxicity endpoints, both *in vitro* and *in vivo*, are included in the systematic data review for ADE development, particularly for, but not limited to, oncology products. Structure- and class-based considerations can be applied for early-stage APIs and/or APIs with limited genotoxicity datasets. Assessment of the MOA for the genotoxic and carcinogenic potential also informs that approach for PoD selection and application for setting the health-based limit. Frameworks for assessing MOA are routinely used for health risk assessment (reviewed in Meek et al., 2014).

In cases of observed (*e.g.,* bacterial reverse mutation) or suspected (*e.g.*, *in silico* predictions) *in vitro* mutagenic potential with unknown *in vivo* carcinogenic potential, it is often appropriate to forgo development of an ADE, and instead, defer to a TTC-based approach as described in ICH M7 for DNA reactive impurities (ICH, 2014b). Examples of TTC-based exposure limits include the value of 1.5 μg/day as outlined in ICH M7 (ICH, 2014b) and the essentially equivalent value of 1 μg/day as described by Dolan et al. (2005) (for more details, see Faria et al., 2016; Hayes et al., 2016; both this issue). The TTC for mutagenic impurities represents a lifetime daily exposure level that is conservatively estimated to be associated with 1×10^{-5} excess lifetime cancer risk. Higher TTC values may be applied to APIs (*e.g.,* investigational APIs) with less-than-lifetime exposure scenarios (ICH, 2014b; Olson et al., 2016, this issue). It is appropriate to apply the TTC to compounds that test positive in the *in vitro* Ames mutagenicity assay in the absence of sufficient *in vivo* rodent carcinogenicity data, compounds for which no threshold for genotoxicity can be identified, or compounds with structure- and/or class-based concerns for which no mutagenicity data are available. For compounds with positive *in vitro* cytogenetics data only, further evaluation of the available data for the compound and/or chemical class is needed prior to ADE determination. That said, it is recognized that other methods/approaches to quantitative analysis of dose-response data from *in vitro* and *in vivo* genotoxicity assays, including the BMD level, the no-observed-genotoxic-effect-level (NOGEL), and the threshold or break-point dose, are currently under evaluation by other working groups for PoD determination (Gollapudi et al., 2013; Johnson et al., 2014; MacGregor et al., 2015a,b).

For compounds that test positive in the *in vitro* Ames mutagenicity assay and for which sufficient *in vivo* rodent carcinogenicity data are available, linear extrapolation from the PoD (*e.g.,* TD_{50} or $BMDL_{10}$) to an accepted excess lifetime cancer risk (1×10^{-5}) can be applied to identify a compound-specific PoD for ADE development.

Where identified, a threshold dose for mutagenicity may also be used as a PoD. Müller and Gocke (2009) described the derivation of an ADE for ethyl methanesulfonate, applying the ICH Q3C(R5) methodology to observed thresholds for both *in vivo* mutagenicity and clastogenicity in mice that were attributed to the saturation of *in vivo* DNA repair processes.

Compounds that test positive in *in vitro* and/or *in vivo* clastogenicity assays and test negative in the *in vitro* Ames mutagenicity assay likely do not react directly with DNA (Sutter et al., 2013). In cases where a threshold mechanism of genotoxicity can be identified, the measured or estimated NOAEL can be used as a PoD in deriving the ADE [as described in ICH M7 following ICH Q3C(R5) methodology (ICH, 2011)]. This approach is appropriate for aneugenic compounds, for example, that test positive in the *in vivo* micronucleus assay.

5.1.3. PoDs for APIs intended for use in serious or life-threatening indications

Although the general principles for PoD selection remain the same for APIs intended for use in serious or life-threatening indications, issues such as lack of a NOAEL or data gaps are more common in such cases. In addition, a higher level of risk to patients is tolerated, *e.g.*, for anticancer APIs given the life-saving nature of such drugs.

Because dose selection during nonclinical and clinical development of APIs intended for use in serious indications is often driven by tolerability and efficacy, and because there may be no regulatory requirement to establish a NOAEL, nonclinical and clinical development often proceeds in the absence of this information. In addition, clinical studies may be limited to patient populations with a relatively high background rate of adverse events or may not include placebo-controlled comparator groups, making it more difficult to establish critical effects appropriate for use in the ADE determination. In such cases it is particularly important to select the PoD based on scientific consideration of the effects anticipated to be most relevant to potentially exposed healthy individuals.

When a NOAEL has not been established, it may be difficult to justify application of the default AF for extrapolation from a LOAEL to a presumed NOAEL for doses associated with severe toxicity (Sussman et al., 2016, this issue). This is because there may be a larger ratio between the therapeutic dose and the NOAEL than accounted for with typical default AF values. In such cases, it may be helpful to consider relevant data from pharmacology or other studies which utilized lower doses. For example, the absence of drug-related clinical pathology changes in an early nonclinical PK study may be used to establish a PoD if one cannot be derived from subsequent toxicity studies performed at higher doses. In other cases, it may be feasible to leverage PD data from nonclinical or clinical studies to establish a dose that is expected to be

pharmacologically inactive. Early involvement and coordination with project development teams may facilitate the inclusion of endpoints useful for deriving a PoD in nonclinical or clinical studies in which lower doses are evaluated.

The derivation of the ADE for direct-acting mutagens or antimitotic agents is largely of historical or legacy interest since most development efforts are now focused on molecules that target specific pathways believed to play key roles in the development or progression of cancer. However, an emerging class of anti-cancer therapies based on such direct-acting agents is the antibody-drug conjugate (ADC), which typically consists of an antibody specific for a tumor cell antigen linked to a nonspecific cytotoxic agent (sometimes referred to as the "warhead" or "toxin"). One such example is Kadcyla® (ado-trastuzumab emtansine), an ADC consisting of a HER2-targeted antibody and microtubule inhibitor that is indicated for the treatment of HER2-positive, metastatic breast cancer. Although the antibody component of the molecule is intended to limit the extent of off-target toxicities at therapeutic doses, target-independent toxicities resulting from nonspecific effects on rapidly dividing cells, such as hematologic or reproductive toxicity, are likely to occur at the relatively high doses used in toxicity studies and in cancer patients. Consequently, it is important to consider the warhead toxicity, stability of the conjugate (*i.e.*, ability to stay connected to the antibody before being released in the target tissue), and the toxicity testing model in which the finding was observed (Gould et al., 2016, this issue). For example, the PoD based on off-target effects in a non-binding species (typically rodent) may be substantially lower than those in a binding species (typically monkey) due to differences in the tissue distribution of the conjugate in each model. An understanding of the stability of the conjugate *in vivo* or data derived from studies with the individual components may also play a role in the assessment if the toxicity is known to be associated with the free toxin rather than the intact conjugate. When taken together, such information can be used to establish the most appropriate PoD to be used in the human health risk assessments.

5.1.4. PoDs for biopharmaceuticals, antibiotics, antivirals, and antifungals

Pharmaceuticals represent a variety of different compound types and mechanisms, and some, such as biopharmaceuticals, antibiotics, antivirals, and antifungals, require special considerations in the selection of the PoD. Selection of the PoD for biopharmaceuticals (*i.e.*, large molecules such as monoclonal antibodies or other therapeutic proteins/peptides) is similar to small molecules with some unique differences in the datasets. As described in ICH S6, some datasets are typically excluded from the nonclinical package such as genotoxicity and carcinogenicity based on the inherent nature of biopharmaceuticals (ICH, 2009). Often these endpoints are of lower concern for biopharmaceuticals. Also, a certain animal model may be considered irrelevant since the biological receptor is not found in the species. The use of transgenic animals containing the receptor or relevant species may be used in derivation of the PoD. In addition, biopharmaceuticals in many cases do not exhibit off-target toxicity but responses due to exaggerated pharmacology. Exaggerated pharmacology can cause toxicity due to "excessive modulation of the activity of the primary pharmacological target beyond the point necessary for efficacy" (Kramer et al., 2007). In these cases, the NOAEL was set at the highest dose but pharmacologic effects were observed at the lower doses, and it is likely that the human data would be more relevant for selection of the PoD. An example of this can be seen in tumor necrosis factor-α (TNF) inhibitors, which can cause immunosuppressive-related adverse effects resulting from exaggerated pharmacology (Vugmeyster et al., 2012).

For antibiotics, antivirals, and antifungals, selection of the PoD should be on a case-by-case basis. As with other drugs, the nonclinical package and clinical adverse effects should be considered to select a PoD. Antibiotics, antivirals, and antifungals target a foreign organism and not the host body. Pharmacology in some of these cases may be irrelevant as there would be no effect in individuals devoid of the foreign organism. Expert judgment may be needed to determine if adverse effects observed in infected patients are relevant to non-infected individuals. However, one may consider, in addition to the standard toxicity considerations, that the residual level would not result in resistance of the foreign organism to further treatments or that the drug does not influence the normal milieu of the body such as antibiotic effects on gut microbiota. Development of a microbiological ADE can be adapted from the veterinary field, where a health-based limit is developed for antibacterial residues in meat using *in vitro* or *in vivo* antimicrobial data (VICH, 2012).

6. Selecting PoDs for pharmaceuticals with data gaps

As pharmaceuticals are developed, there will be missing pieces of data for selection of a PoD (Hayes et al., 2016, this issue). This may mean that the PoD could change as more data become available. In these cases, the PoD may be selected with corresponding protective assumptions given the uncertainty in data. For example, developmental toxicity may not be tested for certain pharmaceuticals, such as those intended to treat advanced cancer, until late in development. However, the mechanism of action of certain experimental APIs may indicate that their pharmacology may impact embryonic development. In these cases, the PoD may be based on pharmacology, recognizing that minimizing potential pharmacological effects will also minimize the risk for developmental toxicity. As there are additional uncertainties with this approach, it may in some cases be appropriate to forgo ADE extrapolation for a hazard banding or TTC approach (Dolan et al., 2005; Faria et al., 2016, this issue; Stanard et al., 2015).

7. Sensitive subpopulations

The ADE is assumed to be protective for all patient populations, including sensitive subpopulations. In some cases, there are data for a specific patient population that should be included in the overall ADE calculation, such as in pediatric patients or juvenile animals (Hayes et al., 2016, this issue). Susceptible subpopulations are also analyzed in clinical trials to ensure certain patients would not be overexposed or react negatively to the medicine. In some cases, patients can be the most susceptible subpopulation as diseased individuals are more susceptible to the drug than healthy individuals. Personalized medicine is designed to be effective only in certain individuals, such as those with specific genomic characteristics. Data from all populations should be analyzed to select the most appropriate PoD for the ADE evaluation. Applying data from sensitive subpopulations to the ADE can reduce the composite AF, especially intra-individual variability (Reichard et al., 2016; Sussman et al., 2016; both this issue).

8. Portal of entry relevance

There are a number of drugs which are intended for treatment of effects with local administration, such as ocular, intra-articular, dermal, *etc*. The nonclinical and clinical studies for these APIs are designed to evaluate safety and efficacy of drugs with such administration and may lack the data about effects with systemic administration. Some suggested techniques for filling in data gaps

are to use the PoD for analogous compounds tested systemically and make appropriate adjustments based on potency and/or kinetics. In addition, a TTC approach, as mentioned above, could be used with expert judgment to determine the potential for toxicity and/or potency if administered systemically. Typically, it is not appropriate to use portal of entry effects as the bases for the PoD without an evaluation of potential systemic effects unless setting an ADE specifically for that intended administration route.

9. Conclusions and outlook

The selection of a PoD in the derivation of an ADE is a complex process that is critical in deriving robust health-based limits. It requires the experience of a qualified individual, who also understands the unique datasets generated in pharmaceutical development. The PoD process involves data collection and hazard characterization, searching for the critical effects, and final selection of the one or more PoDs. In contrast to other classes of chemicals, there are also several endpoints which are unique to pharmaceuticals which should be considered for PoD selection.

The pharmaceutical industry continues to discover and develop new therapies with novel mechanisms. The technology to discover sensitive biomarkers is rapidly improving. Genomics is becoming more important to the development of pharmaceuticals. This evolution is important so that companies can rapidly bring high-quality, life-saving medicines to those who need them. It also provides the toxicologist or expert with new opportunities for refined PoD selection. Best practices for PoD selection must continue to evolve as the science advances and be shared to ensure robust ADEs across the industry. Currently, guidance documents for ADE (and PDE) derivation do not provide specific and harmonized guidance on the selection of appropriate PoDs. Further harmonization in this area will be helpful in implementation of guidelines and in acceptance of derived ADEs across regulatory bodies.

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References

Crump, K.S., 1984. A new method for determining allowable daily intakes. Fundam. Appl. Toxicol. Off. J. Soc. Toxicol. 4, 854–871.

DeBord, D.G., Burgoon, L., Edwards, S.W., Haber, L.T., Kanitz, M.H., Kuempel, E., Thomas, R.S., Yucesoy, B., 2015. Systems biology and biomarkers of early effects for occupational exposure limit setting. J. Occup. Environ. Hyg. 12 (Suppl. 1), S41–S54.

Dolan, D.G., Naumann, B.D., Sargent, E.V., Maier, A., Dourson, M., 2005. Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. Regul. Toxicol. Pharmacol. 43, 1–9. http://dx.doi.org/10.1016/j.yrtph.2005.06.010.

Dorato, M.A., Engelhardt, J.A., 2005. The no-observed-adverse-effect-level in drug safety evaluations: use, issues, and definition(s). Regul. Toxicol. Pharmacol. RTP 42, 265–274. http://dx.doi.org/10.1016/j.yrtph.2005.05.004.

EFSA, 2009. Application of systematic review methodology to food and feed safety assessments to support decision making. European Food Safety Authority (EFSA). EFSA J. 1150, 1–72. Available at: http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/sc_op_ej1150_bmd_en.pdf.

EMA, 2007. Guideline on Strategies to Identify and Mitigate Risks for First-inhuman Clinical Trials with Investigational Medicinal Products. Doc. Ref.EMEA/CHMP/SWP/28367/07. European Medicine Agency (EMA), London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf.

EMA, 2014. Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities. EMA/CHMP/CVMP/SWP/169430/2012. European Medicine Agency (EMA), London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177735.pdf.

EMA, 2015. European Public Assessment Reports. European Medicine Agency (EMA), London. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125.

Faria, E.C., Dolan, D.G., Morinello, E., Pecquet, A.M., Sehner, C., Weideman, P., 2016. Using default methodology to derive the acceptable daily exposure (ADE). Manuscr. Accept. Regul. Toxicol. Pharmacol. (this issue).

Gollapudi, B.B., Johnson, G.E., Hernandez, L.G., Pottenger, L.H., Dearfield, K.L., Jeffrey, A.M., Julien, E., Kim, J.H., Lovell, D.P., Macgregor, J.T., Moore, M.M., van Benthem, J., White, P.A., Zeiger, E., Thybaud, V., 2013. Quantitative approaches for assessing dose-response relationships in genetic toxicology studies. Environ. Mol. Mutagen 54, 8–18. http://dx.doi.org/10.1002/em.21727.

Gould, J.C., Kasichayanula, S., Shepperly, D.C., Boulton, D.W., 2013. Use of low-dose clinical pharmacodynamic and pharmacokinetic data to establish an occupational exposure limit for dapagliflozin, a potent inhibitor of the renal sodium glucose co-transporter 2. Regul. Toxicol. Pharmacol. RTP 67, 89–97. http://dx.doi.org/10.1016/j.yrtph.2013.07.002.

Gould, J.C., Callis, C., Dolan, D.G., Stanard, B., Weideman, P., 2016. Special endpoint and product specific considerations in pharmaceutical ADE derivation. Manuscr. Accept. Regul. Toxicol. Pharmacol.

Hayes, E.P., Faria, E.C., Jolly, R., Lovsin Barle, E., Molnar, L., Naumann, B.D., Olson, M., Pecquet, A.M., Shipp, B., Weideman, P., 2016. Harmonization effort for acceptable exposure methodology applied to pharmaceutical cleaning validation-operational aspects. Manuscr. Accept. Regul. Toxicol. Pharmacol.

ICH, 2005. Ich harmonised tripartite guideline, quality risk management Q9. In: International Conference on Harmonisation (ICH), Geneva. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf.

ICH, 2009. S9 Nonclinical evaluation for anticancer pharmaceuticals. In: International Conference on Harmonisation (ICH), Geneva. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S9/Step4/S9_Step4_Guideline.pdf.

ICH, 2011. Impurities: guideline for residual solvents Q3C(R5) step 4 version. In: International Conference on Harmonisation (ICH), Geneva. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Step4/Q3C_R5_Step4.pdf.

ICH, 2014a. Ich Q3D technical document Q3D: guideline for elemental impurities. Current Step 4 version; Dated: 16 Dec 2014. In: International Conference on Harmonisation (ICH), Geneva. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D_Step_4.pdf.

ICH, 2014b. Ich guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. In: International Conference on Harmonisation (ICH), Geneva. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf.

IPCS, 2005. Chemical-specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/concentration-response Assessment. International Programme on Chemical Safety (IPCS). World Health Organization (WHO), Geneva. Available at: http://www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf.

ISPE, 2010. Baseline Pharmaceutical Engineering Guide. In: Risk-based Manufacture of Pharmaceutical Products: a Guide to Managing Risks Associated with Cross Contamination, vol. 7. International Society for Pharmaceutical Engineering (ISPE), Tampa, FL. Available at: http://www.ispe.org/baseline-guides/risk-mapp.

Johnson, G.E., Soeteman-Hernández, L.G., Gollapudi, B.B., Bodger, O.G., Dearfield, K.L., Heflich, R.H., Hixon, J.G., Lovell, D.P., MacGregor, J.T., Pottenger, L.H., Thompson, C.M., Abraham, L., Thybaud, V., Tanir, J.Y., Zeiger, E., van Benthem, J., White, P.A., 2014. Derivation of point of departure (PoD) estimates in genetic toxicology studies and their potential applications in risk

assessment. Environ. Mol. Mutagen 55, 609–623. http://dx.doi.org/10.1002/em.21870.
Kramer, J.A., Sagartz, J.E., Morris, D.L., 2007. The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates. Nat. Rev. Drug Disc. 6, 636–649.
Lewis, R.W., Billington, R., Debryune, E., Gamer, A., Lang, B., Carpanini, F., 2002. Recognition of adverse and nonadverse effects in toxicity studies. Toxicol. Pathol. 30, 66–74.
MacGregor, J.T., Frötschl, R., White, P.A., Crump, K.S., Eastmond, D.A., Fukushima, S., Guérard, M., Hayashi, M., Soeteman-Hernández, L.G., Johnson, G.E., Kasamatsu, T., Levy, D.D., Morita, T., Müller, L., Schoeny, R., Schuler, M.J., Thybaud, V., 2015a. IWGT report on quantitative approaches to genotoxicity risk assessment II. Use of point-of-departure (PoD) metrics in defining acceptable exposure limits and assessing human risk. Mutat. Res. Genet. Toxicol. Environ. Mutagen 783, 66–78. http://dx.doi.org/10.1016/j.mrgentox.2014.10.008.
MacGregor, J.T., Frötschl, R., White, P.A., Crump, K.S., Eastmond, D.A., Fukushima, S., Guérard, M., Hayashi, M., Soeteman-Hernández, L.G., Kasamatsu, T., Levy, D.D., Morita, T., Müller, L., Schoeny, R., Schuler, M.J., Thybaud, V., Johnson, G.E., 2015b. IWGT report on quantitative approaches to genotoxicity risk assessment I. Methods and metrics for defining exposure-response relationships and points of departure (PoDs). Mutat. Res. Genet. Toxicol. Environ. Mutagen 783, 55–65. http://dx.doi.org/10.1016/j.mrgentox.2014.09.011.
Meek, M.E., Lipscomb, J.C., 2015. Gaining acceptance for the use of in vitro toxicity assays and QIVIVE in regulatory risk assessment. Toxicol 332, 112–123. http://dx.doi.org/10.1016/j.tox.2015.01.010.
Meek, M.E., Palermo, C.M., Bachman, A.N., North, C.M., Lewis, R.J., 2014. Mode of action human relevance (species concordance) framework: evolution of the Bradford Hill considerations and comparative analysis of weight of evidence. J. Appl. Toxicol. 34, 595–606. http://dx.doi.org/10.1002/jat.2984.
Müller, L., Gocke, E., 2009. Considerations regarding a permitted daily exposure calculation for ethyl methanesulfonate. Toxicol. Lett. 190, 330–332. http://dx.doi.org/10.1016/j.toxlet.2009.03.015.
Naumann, B.D., Sargent, E.V., 1997. Setting occupational exposure limits for pharmaceuticals. Occup. Med. Phila. Pa 12, 67–80.
Olson, M., Faria, E.C., Hayes, E.P., Jolley, R., Lovsin Barle, E., Molnar, L., Naumann, B.D., Pecquet, A.M., Shipp, B., Weideman, P., 2016. A harmonization effort for acceptable exposure methodology applied to pharmaceutical cleaning validation- communication with external stakeholders. Manuscr. Accept. Regul. Toxicol. Pharmacol.
Reichard, J.F., Maier, M.A., Naumann, B.D., Pecquet, A.M., Pfister, T., E.P, Sandhu, R., Sargent, E.V., Streeter, A.J., Weideman, P., 2016. Toxicokinetic and toxicodynamic considerations when deriving health-based exposure limits for pharmaceuticals. Manuscr. Accept. Regul. Toxicol. Pharmacol.
Rhomberg, L.R., Goodman, J.E., Bailey, L.A., Prueitt, R.L., Beck, N.B., Bevan, C., Honeycutt, M., Kaminski, N.E., Paoli, G., Pottenger, L.H., Scherer, R.W., Wise, K.C., Becker, R.A., 2013. A survey of frameworks for best practices in weight-of-evidence analyses. Crit. Rev. Toxicol. 43, 753–784. http://dx.doi.org/10.3109/10408444.2013.832727.
Rowland, M., Tozer, T.N., 1980. Clinical Pharmacokinetics: Concepts and Applications, first ed. Lea and Febiger, Philadelphia, PA.
Sandhu, R., Willis, A.M., Lee, D., Gadagbui, B., Reichard, J., Maier, A., 2014. A decision tree to optimize literature identification for pharmaceutical risk assessments. In: Toxicology Excellent for Risk Assessment (TERA) and the University of Cincinnati, Presented at the Society of Toxicology Meeting, 2014. Phoenix, Arizona.
E.R. Squibb & Sons, L.L.C, 2014. Prescribing Information for Farxiga (Dapagliflozin) Tablet, Film Coated.
Stanard, B., Dolan, D.G., Hanneman, W., Legare, M., Bercu, J.P., 2015. Threshold of toxicological concern (TTC) for developmental and reproductive toxicity of anticancer compounds. Regul. Toxicol. Pharmacol. RTP 72, 602–609. http://dx.doi.org/10.1016/j.yrtph.2015.05.024.
Sussman, R.G., Naumann, B.D., Pfister, T., E.P, Sehner, C., Weideman, P., 2016. A harmonization effort for exposure methodology – considerations for application of adjustment factors. Manuscr. Accept. Regul. Toxicol. Pharmacol.
Sutter, A., Amberg, A., Boyer, S., Brigo, A., Contrera, J.F., Custer, L.L., Dobo, K.L., Gervais, V., Glowienke, S., van Gompel, J., Greene, N., Muster, W., Nicolette, J., Reddy, M.V., Thybaud, V., Vock, E., White, A.T., Müller, L., 2013. Use of in silico systems and expert knowledge for structure-based assessment of potentially mutagenic impurities. Regul. Toxicol. Pharmacol. RTP 67, 39–52. http://dx.doi.org/10.1016/j.yrtph.2013.05.001.
Travis, K.Z., Pate, I., Welsh, Z.K., 2005. The role of the benchmark dose in a regulatory context. Regul. Toxicol. Pharmacol. RTP 43, 280–291. http://dx.doi.org/10.1016/j.yrtph.2005.07.003.
US EPA, 2012. Benchmark Dose Technical Guidance. Risk Assessment Forum. U.S. Environmental Protection Agency. EPA/100/R-12/001.
US FDA, 2005. Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research, Silver Spring, MD. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078932.pdf.
US FDA, 2012. Drug Approvals and Databases - Drugs@FDA Glossary of Terms. U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research, Silver Spring, MD. Available at: http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm (Silver Spring, MD).
VICH, 2012. VICH 36(R). Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI. Veterinary International Cooperation on Harmonisation (VICH), U.S. Department of Health and Human Services. Available at: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM124674.pdf.
VICH, 2015. Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish an Acute Reference Dose (ARfD). Draft Guidance, VICH GL54. Veterinary International Cooperation on Harmonisation (VICH), U.S. Food and Drug Administration. Available at: http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm448430.pdf.
Vugmeyster, Y., Xu, X., Theil, F.-P., Khawli, L.A., Leach, M.W., 2012. Pharmacokinetics and toxicology of therapeutic proteins: advances and challenges. World J. Biol. Chem. 3, 73–92. http://dx.doi.org/10.4331/wjbc.v3.i4.73.