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Application of the threshold of toxicological concern concept when applied to pharmaceutical manufacturing operations intended for short-term clinical trials

Joel P. Bercu *, David G. Dolan

Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, United States

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ABSTRACT

In the manufacture of pharmaceuticals, if a multiproduct facility shares equipment amongst drug substances/products it is incumbent upon the manufacturer to demonstrate removal of the pharmaceutical through a robust cleaning validation/verification program. Removal must be to below limits considered acceptable from a quality and toxicological perspective. In order to address the toxicological concerns, an acceptable daily exposure (ADE) was developed which is the "dose that is unlikely to cause an adverse effect if ... exposed, by any route ... at or below this dose every day for a lifetime" (ISPE, 2010). For compounds in development, defaulted ADEs were proposed by Dolan et al. (2005) and adopted by the International Society of Pharmaceutical Engineers (ISPE) as conservative cutoffs for compounds with limited data. In Phase 1 clinical trials, exposure is typically short-term (single dose or repeated doses for $\leq$30 days) compared to the chronic doses used to derive ADE and defaulted ADEs. An analysis of publicly available databases for toxicological and pharmacological effects supports the use of 10-fold higher defaulted values when the residual drug substance is in a developmental pharmaceutical intended for Phase 1 clinical trials (exposure $\leq$30 days).

1. Introduction

In the manufacture of pharmaceuticals, if a multiproduct facility shares equipment amongst drug substances it is incumbent upon the manufacturer to demonstrate removal of the pharmaceutical through a robust cleaning validation/verification program. Removal must be to below limits considered acceptable from a quality and toxicological perspective. Toxicological risk assessment practices have been developed by the International Society of Pharmaceutical Engineers (ISPE) (ISPE, 2010). As part of the process, an acceptable daily exposure (ADE) was developed, which is the "dose that is unlikely to cause an adverse effect if an individual is exposed, by any route (e.g., intrathecal, inhaled), at or below this dose every day for a lifetime. By definition, a robust ADE limit should be established with pertinent toxicological data and it should be protective of all populations by all routes of administration" (ISPE, 2010). The ADE is then used to determine the maximum allowable carryover (MAC) that is allowed from one drug substance or drug product into another (the term drug substance is used in this manuscript to denote the active pharmaceutical ingredient).

The approval of new drug products requires several years to develop the nonclinical (e.g., animal) and clinical testing data required to demonstrate both safety and efficacy. Therefore, drug substances early in development have less drug substance-specific data available to develop an ADE than those that have progressed to Phase II, Phase III, or marketing approval. As a result, Dolan et al. (2005) developed methodology for determining ADEs based on limited data which was then adopted by ISPE (Dolan et al., 2005; ISPE, 2010). The methodology uses the concept called the threshold of toxicological concern (TTC), which is a default cutoff based on a database of known toxicants to conservatively protect from exposure to a chemical when the toxicity is unknown (Kroes et al., 2004). The TTC concept is not novel to pharmaceuticals as it was originally developed for indirect food additives and has been applied to other areas such as cosmetics (Cheeseman et al., 1999; Kroes et al., 2004, 2007; Munro et al., 1999). Based on the toxicity of industrial chemicals and pharmaceuticals, TTC cutoff values were developed as described in Table 1 (Dolan et al., 2005).

If a drug substance shares equipment with another that is intended for Phase 1 clinical trials, then there is toxicological justification for a higher limit. Exposure durations of drug substances early in development intended for Phase I clinical trials are not

Abbreviations: ADE, acceptable daily exposure; EMA, European Medicines Agency; ICH, International Conference on Harmonisation; ISPE, International Society of Pharmaceutical Engineers; MAC, maximum allowable carryover; MRTD, maximum recommended therapeutic dose; NOEL, no observed effect level; PDE, permitted daily exposure; TTC, threshold of toxicological concern; QSAR, quantitative structure activity relationship; USFDA, United States Food and Drug Administration.

* Corresponding author. Fax: +1 805 498 8564.
E-mail addresses: jbercu@amgen.com, jsbercu@hotmail.com (J.P. Bercu).

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Table 1
ADE default cutoffs assuming lifetime exposure based on Dolan et al. (2005).

Category	ADE
Compounds that are not likely to be potent, highly toxic or carcinogenic	100 μg/day
Compounds that may be potent or highly toxic	10 μg/day
Compounds that are mutagenic or may be carcinogenic	1 μg/day

chronic but limited to a short duration (≤30 days). For example, in the single-dose safety study volunteers receive one dose and in the multi-dose safety study they receive more than one dose over the course of a few days. ISPE recognized that higher ADE values can be developed for certain exposure scenarios and patient populations (ISPE, 2010). The TTC values developed by Dolan et al. (2005) were intended for chronic exposure durations. The authors envisioned that higher ADE default values could be allowed for short-term exposure, but no specific methodology was proposed.

The toxicology of a compound depends on both the dose and the duration of exposure. This concept was developed in the 1920s and is referred to as Haber's rule which is mathematically described as $c \times t = k$, where c = concentration, t = time, and k = constant, wherein the incidence or severity of an adverse health effect is a function of total exposure to a compound (Haber, 1924). This concept continues to be a scientific paradigm in toxicology-based risk assessment (Felter et al., 2011; Gaylor, 2000; Rozman and Doull, 2001a). It is also integrated as part of regulatory documents as a safety factor of 3–10-fold is considered appropriate for extrapolating short-term to long-term exposures (ICH, 2011; USEPA, 2002). This concept has been applied to pharmaceutical impurities, as in the ICH Q3C(5) guideline for residual solvents or the TTC values derived for genotoxic impurities (EMA, 2006; ICH, 2011; USFDA, 2008). For residual solvents, the permissible daily exposure (PDE) is similar to the ADE as it is the "maximum acceptable intake per day of residual solvent in pharmaceutical products" derived from toxicology data and is a lifetime exposure estimate. The PDE is derived preferably by dividing the no-observable effect level (NOEL) by appropriate modifying factors (also known as "uncertainty factors," and "safety factors"). One modifying factor (F3, "A variable factor to account for toxicity studies of short-term exposure") ranges from 1–10 to extrapolate from short-term to chronic exposure. For genotoxic impurities in pharmaceuticals, often there are limited data to perform a toxicological assessment and the TTC concept is also applied to determine the acceptable dose. It was recognized by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) that higher TTC daily doses (termed "staged TTC") are acceptable for clinical trials when compared to chronic use (EMA, 2008; Muller et al., 2006; USFDA, 2008) (Table 2).

The purpose of this report is to determine if a higher default ADE for small molecule (i.e., synthetic chemical) drug substances based on the TTC principle can be developed for multi-product facilities where the drug sharing equipment is intended for Phase I clinical trials, and if so, what specific values or approaches may be used to derive a protective value. Since a safety factor as high as 10-fold is used to extrapolate from short-term to chronic use applications, the initial hypothesis was that a 10-fold higher value would be considered acceptable from a toxicological perspective.

Table 3
Description of Cramer structural classification used in the Munro database.

Class	Description
Class 1	Substances with simple chemical structures and for which efficient modes of metabolism exist, suggesting a low order of oral toxicity
Class 2	Substances which possess structures that are less innocuous than class I substances, but do not contain structural features suggestive of toxicity like those substances in class III
Class 3	Substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups

2. Methods

2.1. Munro database

The Munro database contains three classes developed by Cramer et al. (1978) which are described in Table 3 (Cramer et al., 1978). Each compound in the Munro database was segregated into one of the three classes based on potential toxicity from its structure. Animal studies were analyzed by Munro et al. (1996) and a NOEL was calculated for each compound (Munro et al., 1996).

A curated database based on the Munro et al. (1996) study was downloaded from a scientific report submitted to the European Food Safety Authority Publication (Bassan et al., 2011). As represented in Table 4, subchronic data were specifically segregated and used for the evaluation. Studies with exposure durations from 60 to 365 days were considered subchronic. In addition, reproductive and developmental effects can occur from brief exposure periods ("windows of vulnerability") of a chemical so these data were also included in the analysis. Reproductive and developmental studies included in the database were those studies that evaluated reproductive parameters (e.g., fertility, reproductive organs), and studies that evaluated teratogenicity. The exposure durations for reproductive and developmental studies were not specified. While these studies were longer than a typical Phase I study, these longer duration animal studies were considered a conservative estimate of repeated-dose, short-term exposure. A total of 613 compounds were in the Munro database, and this study used 67% of the compounds to evaluate subchronic/reproductive toxicity.

A short-term ADE was developed for each compound in the Munro database. The short-term ADE was considered an appropriate limit for exposure of a limited duration such as that occurring in Phase 1 clinical trials. The short-term ADE was determined by dividing the calculated NOEL by 100 for each compound. The percent of compounds was determined whose new proposed default limits were less than their calculated short-term ADE.

2.2. FDA maximum recommended therapeutic dose (MRTD) database

The maximum recommended therapeutic dose (MRTD) database was developed by the United States Food and Drug

Table 2
Higher acceptable daily intakes recommended by EMA for genotoxic impurities during clinical trials.

	Duration of clinical trial exposure					
Acceptable daily intake (μg/day)	Single dose	≤1 month	≤3 months	≤6 months	≤12 months	>12 months
	120	60	20	10	5	1.5

Note approach similar to USFDA draft guidance with some slight differences. The term acceptable daily intake (ADI) was used instead of ADE. Both terms have a similar meaning but ADE has been used for cleaning validation/verification.