A Novel Method for Assessing Drug Degradation Product Safety Using Physiologically-Based Pharmacokinetic Models and Stochastic Risk Assessment

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ABSTRACT: Patient safety risk due to toxic degradation products is a potentially critical quality issue for a small group of useful drug substances. Although the pharmacokinetics of toxic drug degradation products may impact product safety, these data are frequently unavailable. The objective of this study is to incorporate the prediction capability of physiologically based pharmacokinetic (PBPK) models into a rational drug degradation product risk assessment procedure using a series of model drug degradants (substituted anilines). The PBPK models were parameterized using a combination of experimental and literature data and computational methods. The impact of model parameter uncertainty was incorporated into stochastic risk assessment procedure for estimating human safe exposure levels based on the novel use of a statistical metric called "PROB" for comparing probability that a human toxicity-target tissue exposure exceeds the rat exposure level at a critical no-observed-adverse-effect level. When compared with traditional risk assessment calculations, this novel PBPK approach appeared to provide a rational basis for drug instability risk assessment by focusing on target tissue exposure and leveraging physiological, biochemical, biophysical knowledge of compounds and species. J Pharm Sci 104:3101–3119, 2015
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INTRODUCTION

A fundamental requirement for the licensure of pharmaceutical products is that their quality attributes (including potency and purity) are maintained throughout their manufacturing, shipping, and storage. A drug substance may generate toxic impurities via hydrolytic and/or oxidative degradation, whereby, not only the rate of drug potency loss but also the rate of degradant accumulation may impact safety/toxicity risks and thereby determine drug product stability requirements. The accumulation of toxic degradation products is a critical quality issue for a small group of useful drug products, for example, lidocaine, isoniazid, chlorhexidine, and gabapentin.[1] In recent years, genotoxicity and/or carcinogenicity of drug impurities have received considerable attention by industrial and regulatory scientists.[2–4] While investigating the correlation between chemical structure and DNA activity for about 300 compounds based on a Salmonella carcinogenicity assay, Ashby [5] introduced the concept of the structural alert. According to these investigators, structural alerts are molecular substructures of a compound whose presence correlates with carcinogenicity. Using degradation product prediction software for a variety of drug substances, Raillard et al.[1] conducted a study to evaluate the potential of genotoxicity that may arise from drug degradation in the form of structural alerting molecules. Approximately 70% of the structural alerts found in their analysis were aldehydes, α,β-unsaturated carbonyls, and primary aromatic amines.

For drug products that give rise to potential toxic degradation products, the critical stability limit is typically not 5%–10% potency loss but rather <1% conversion of the drug substance to its degradation product. For example, gabapentin lactam has been reported to be 20-fold more toxic than its parent drug,[6] thus the United States Pharmacopeia (USP) limit for the dehydration product of gabapentin degradation is 0.4%.[7,8] The USP limit for p-chloroaniline (PCA) in chlorhexidine oral rinse solutions is 3 ppm.[7] The allowable limit for p-aminophenol (PAP) in acetaminophen bulk powder is 0.004%.[7]

The International Committee on Harmonization (ICH) and the United States Food and Drug Administration (US FDA) have published guidelines for the identification and qualification of impurities in new drug substances and drug products.[3,4,9] For degradation products, the ICH Guidance Q3B (R2)[4] provides recommendations for reporting, control, identification, and qualification in drug products. The critical value for reporting impurities ranges from 0.05% to 0.1%. Identification is required for any degradation product present at a level greater than the identification threshold, which is typically between 0.1% and 0.5% depending on the daily drug dose. Qualification is the process of evaluating safety data and establishing acceptance criteria for a degradation product. A degradation product should be qualified if it exceeds the qualification threshold, which is typically from 0.15% to 1%.

For a given degradation product, its acceptance criteria (allowable level) is typically no higher than its qualified level based on safety considerations.[4] For many drug products, the

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degradation product limits can be justified based on the levels of the degradant present in preclinical and clinical trial drug product batches.

The guidance from US FDA and ICH provides a clear approach to control drug degradation products. However, it does not provide a rationale, scientific or otherwise, for establishing degradation product acceptance criteria for those exceeding qualification thresholds or for potentially toxic compounds. This leaves the challenge of determining safe levels and ultimately setting acceptance criteria an open problem in risk assessment. The problem can be rationally partitioned into two parts: (1) accurately defining the risk and (2) deciding how much risk is acceptable. At the heart of the acceptance criteria will always be some level of subjective choice: the amount of risk one is willing to accept is personal. It is the goal of this paper to introduce a method of assessing this risk using as much information as possible so that a scientifically sound basis for the risk acceptance criteria can be made.

Traditionally, animal studies have served as the basis for most quantitative risk analysis and require interspecies extrapolation for human health applications. In the standard paradigm for non-cancer risk assessment, test animals are assigned to treatment (dose-level) and control groups. Dose amounts and route of administration are consistent with the intended use of the drug for humans. For each group, toxicity indicators such as body weight (BW), biochemical parameters (e.g., albumin, glucose, and bilirubin), or adverse biological effects are measured. The result is a typical dose–response experiment wherein the percent of animals with critical adverse effect is displayed as function of different doses of toxicant. The statistically significant responses are determined by comparison of each treatment group with the control group. The highest non-statistically significant treatment group response compared with control group response is designated as the "no observed adverse effect level" (NOAEL).[10]

Reference dose (the maximum acceptable human dose of a toxic substance) is typically calculated as a single point estimate by dividing the animal NOAEL value by a series of "uncertainty factors" that are intended to account for potential sources of "unknown" variability such as extrapolation from animals to humans, human population variability, extrapolation from short to long duration of exposure, and database limitations due to the experimental design or analytical techniques.[11] Typically, each uncertainty factor is arbitrarily assigned a numerical value; a value of 10 is common. The effects of compound-specific biological complexities and pharmacokinetics are typically not part of the risk calculations. In addition, the selection of uncertainty factors typically does not consider chemical-specific toxicity mechanisms or pharmacokinetic data.[11] Therefore, these default approaches may not be sufficiently health protective or may be overly conservative.[12]

Incorporating xenobiotic-specific pharmacokinetic data by using physiologically-based pharmacokinetic (PBPK) modeling has been advocated as an alternative to conventional risk assessment methods for the impact of environmental toxicants on human safety. The motivation for using PBPK models is to leverage knowledge about the biology of the test species and compound-specific properties into risk calculations, thereby realistically accounting for uncertainty and variability in the human risk estimates.[12–16] Moreover, because the parameters in a PBPK model have a biological correspondence, they provide a useful framework for evaluating the impact of physiological and pharmacokinetic variability on the uncertainty of individual patient risks.[17] To be sure, predicted exposure following a dose can no longer be imagined as a perfectly known quantity, but must rather be considered a probability distribution representing our degree of belief about the actual value spread out such that the uncertainty in the inputs of the model is propagated to the results. It is this uncertainty in the exposure that requires us to accept some risk. Typically, the PBPK model is used to calculate several plausible exposure metrics which are required to conduct the risk assessment. Depending on the toxicity mechanism of chemical, AUC or maximum concentration of parent drug in target tissue, or the amount of metabolite in target tissue over a period of time, can be selected as exposure metrics.[12]

Implicit in the application of PBPK models in risk assessment is the assumption that equal target tissue exposure across species results in the same toxic effect. Where possible, this should be supported by available toxicodynamic/pharmacodynamic data. In the absence of such data, PBPK models can be used to simulate dose–response models while addressing some of the uncertainty and variability related to pharmacokinetics and pharmacodynamics of chemicals across species.[12] The remaining uncertainty associated with the lack of mechanistic toxicological knowledge needs to be considered in risk assessment.

The objective of our work was to develop a rational and quantitative process for leveraging compound-specific pharmacokinetic information in combination with stochastic risk metrics to estimate human safe dose (exposure levels) for drug degradation products using a series of chemically related model compounds. We chose a series of substituted anilines as model compounds because they have been reported to be degradation products of commercially available drug products, known or potential toxicants, and structurally similar to aniline, which has been the subject of some detailed environmental toxicology studies.

Our work is novel in its application of PBPK model-based risk assessment and the use of the PROB statistic to the problem of developing meaningful specifications for drug degradation products.

METHODS

Overview of the Risk Assessment Process

Our approach was to construct PBPK models for rat and human and to use the models to generate toxicity target tissue exposure distributions as a function of exposure (dose) levels using Monte Carlo (MC) sampling to realistically account for model parameter uncertainty. Then, the human reference exposure level was determined using a statistical metric called PROB, which provides a measure of the position of two distributions in stochastic terms. In the context of safety risk assessment, the PROB value provides a quantitative measure of the risk that human exposure to a potential drug degradation product toxicant at a specific dose level will be greater than for a rat at the critical exposure dose (the no-observed-adverse-effect-level).

The process that we employed was to use a combination of literature and *in vitro* experimentation to obtain initial pharmacokinetic parameters to populate the rat and human PBPK models. Sensitivity and uncertainty analysis were used to evaluate the impact of model parameters on pharmacokinetic tissue