The use of pharmacokinetic and pharmacodynamic data in the assessment of drug safety in early drug development

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The pharmaceutical industry continues to look for ways to reduce drug candidate attrition throughout the drug discovery and development process. A significant cause of attrition is due to safety issues arising either as a result of animal toxicity testing or in the clinical programme itself. A factor in the assessment of safety during early drug development is the pharmacokinetic profile of the compound. This allows safety data to be considered in the light of systemic drug exposure and therefore permits a quantitative assessment. This is particularly applicable when assessing the risk of a new chemical entity (NCE) in relation to safety parameters such as QT interval prolongation, where free plasma concentrations have been shown to be predictive of this property in relation to potency in preclinical testing. Prior to actual human exposure it is therefore important to be able to predict reliably the pharmacokinetic behaviour of an NCE in order to place such safety findings into a quantitative risk context. The emerging science of pharmacogenetics is likely to further our ability to assess the risk of NCEs to populations and individuals due to genetic variance. The drug metabolizing enzyme CYP2D6 has been recognized as providing the potential to result in widely differing systemic drug exposure in the patient population due to polymorphic expression. Further knowledge is likely to add to our understanding of population differences in exposure and response and aid in the identification of risk factors. One potential strategy for improving the effectiveness of the drug discovery process is to obtain clinical pharmacokinetic data more rapidly in order to assess more accurately the potential for both efficacy and safety of an NCE. Whilst procedures and technologies are available that allow this on the microdose scale, it is important that we recognize potential limitations of these approaches in order that they can be applied beneficially.

Introduction
The cost and time taken to bring new medicines to the market has continued to rise over recent times [1, 2] whilst the number of new drug approvals has declined [3]. In order to try to maximize return on investment the pharmaceutical industry is generally looking to improve success rates and reduce candidate attrition during the drug development process. Early termination of drug development programmes that will ultimately fail is seen as an approach that leads to overall cost reduction [2]. In order to achieve this it is important to understand the root causes of attrition that have led to drug development failure in the past. A previously published survey on the causes of failure in drug development (Figure 1) indicated that inappropriate pharmacokinetics were a major cause [4]. Inappropriate pharmacokinetic behaviour includes such factors as low bioavailability due to high extraction or poor absorption characteristics, short elimination half-life leading to short duration of action and excessive variability due to genetic or environmental factors. This observation has led to an increased emphasis on pharmacokinetic input...