Physiologically-based Pharmacokinetic Modelling for the Reduction of Animal Use in the Discovery of Novel Pharmaceuticals

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Summary — The challenges of physiologically-based pharmacokinetic (PBPK) modelling and approaches to replacing the use of animals, in order to determine drug pharmacokinetics, are discussed. Reference is made to the limitations of in vivo animal studies in drug discovery. In particular, the ways in which animal studies contribute to drug attrition during the post-preclinical phase of testing are considered.

Key words: drug discovery, PBPK, pharmaceuticals, replacement.

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Introduction

The pharmaceutical industry performs a large number of live animal studies across a range of activities, particularly in the research and development (R&D) of novel pharmaceuticals. A timeline of events that are associated with the discovery and development of new drugs is shown in Figure 1, along with indications of the proportion of the total number of animals used at each stage of the process. The figure indicates that supposedly poor candidate compounds are progressively eliminated from further research. This compound selection is based on target-binding and modulation studies, which are followed by the structural refinement of a lead compound in order to increase its efficacy and/or address safety concerns. When the average number of compounds that could be investigated at each stage, in order to achieve progression of a certain number of compounds to the next stage, is considered, the following numbers are obtained: of an initial one-million compounds screened, 1000 hits might be identified, of which about 200 might be preclinically evaluated for safety and efficacy.

Animals are mostly used in the preclinical phase, especially during lead identification (LI) and lead optimisation (LO), where many compounds are tested and the great majority are discarded. Hence, it can be seen that animal studies are used to screen out unsuitable compounds very early on in the drug discovery pipeline, when the need for high predictivity is less stringent. However, as a result, even if a useful new drug emerges from the development pipeline, up to 99% of all animal studies will have been undertaken on compounds that will not progress to the clinic, because they will have been assessed as being unsuitable. To give an idea of the scale involved, the total number of animals used globally for in vivo studies each year is estimated at about 48–49 million, with pharmaceutical industry R&D accounting for up to approximately 17-million of these animals (1). If LI and LO account for 60–80% of this number (Figure 1), this corresponds to up to about 10–14 million animals. One of the most disconcerting facts is that, despite this high level of animal experimentation, drug failures occur during each stage of drug development, primarily because of an insufficient understanding of the outcome of introducing a new chemical compound into the human body. Currently, around 90% of potential new drugs will be discontinued from development after progressing to human clinical studies, or by the registration stage (2). The ability to predict human clinical responses to new drugs from corresponding in vivo animal studies can potentially be compromised by any number of differences between the species. These disparities can affect the absorption of the drug from the site of administration into the bloodstream, and how the drug is distributed throughout the body. Once the drug has reached its target site or an unintended (off-target) site, the manner in which it binds and elicits biochemical, physiological and other responses, either direct or indirect, can also vary between species. Of particular note is that the metabolism of the compound, in the liver and/or other organs, can vary dramatically between species. This, in turn, can affect pharmacological activity, toxicity and elimination of the compound and/or its metabolites. Consequently, it can be