A Human Approach to Drug Development: Opportunities and Limitations

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Summary — The pharmaceutical industry is failing in its primary function, with increasing expenditure and decreased output in terms of new medicines brought to market. It cannot carry on as it is, without sliding into a terminal decline. It must, therefore, take some positive steps toward addressing its problems. We do not have to look far to see one very obvious problem, namely, the industry’s continuing reliance on non-human biology as the basis of its evaluation of potential safety and efficacy. The time has come to focus on the relevant, and to realise that more human-based testing is essential, if the industry is to survive as a source of innovation in drug therapy. This can incorporate earlier clinical testing, in the form of microdosing, and promotion of the development of more-powerful computational approaches based on human information. Fortunately, headway is being made in both approaches. However, a problem remains in the lack of functional evaluation of human tissues, where the lack of commitment, and the inadequacy of the tissue resource itself, are hampering any serious developments. An outline of a collaborative scheme is proposed, that will address this issue, central to which is improved access to research tissues from heart-beating organ donors.

Key words: drug development, human tissues, pharmaceutical industry.

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Introduction

It is now well accepted that the pharmaceutical industry is failing in its attempts to identify safe and effective new medicines for the treatment of human disease (1). There are many reasons for this difficulty, but one key problem is undoubtedly the pivotal role played by experimental animals and animal models of human disease (2). While the most widely used species in safety and toxicity testing are the rat and the dog, an objective assessment of their predictive value with regard to safety in human patients is unimpressive and, in some cases, the predictions obtained are downright misleading (3–5). In the face of this unreliability, companies resort to the use of non-human primates as human surrogates, but, in many cases, they have proved to be as unreliable as non-primate species (2, 6). This issue was clearly highlighted by the failure of tests in non-human primates to predict the catastrophic effects of the CD28-SuperMAB, TGN1412, in human volunteers (7). As the drugs in question are intended for human use, it seems obvious that the most appropriate models in which to evaluate efficacy and safety should be human-based and, in view of the industry’s problems, it is unclear why more effort is not channelled in this direction.

Human-based Studies: What Can Be Done?

The key questions are, of course, what human-based studies are feasible, and how can they be performed? Human-based studies can be classified into three broad categories: in vivo, in silico, and in vitro. The first two are increasingly being used, with some success.

— In vivo: Information as to the likely metabolism of a new drug, indicating possible safety issues in patients, can be determined at an early stage through the use of microdosing in human volunteers. This involves the testing, in humans, of doses about 100-fold lower than the anticipated minimum therapeutically-active dose (8, 9). Microdosing, in association with sensitive accelerator mass spectrometry (AMS) technology, has been shown to be capable of providing valuable insight into the way a drug is likely to be handled by the body when dosed within the therapeutic range. Although this approach has only been introduced relatively recently, there is growing evidence of its predictive value (10). It is significant that the Food and Drug Administration (FDA) is now welcoming exploratory Investigational New Drug (IND) submissions as a way of accelerating the drug development process.

— In silico: In vitro testing of cell lines and tissue cultures, especially human cell lines and tissue cultures, has become a widely used in vitro test system for the evaluation of potential drug-induced cytotoxicity and cell death. However, the use of in vitro models to predict human toxicity remains controversial, and it is important to consider the limitations of these models. Animal models, particularly rodents, are often used to test potential drugs before human testing, but the results from these tests may not always accurately predict human toxicity. It is essential to consider the strengths and weaknesses of different models and to use a combination of approaches to ensure the most accurate predictions.

— In vitro: In vitro testing using cell cultures and tissue slices allows for the study of drug metabolism and drug interactions at a cellular level. This approach is particularly useful for studying the effects of drugs on specific cell types and for investigating the mechanisms of action of drugs.

In conclusion, a human-based approach to drug development is necessary to ensure the safety and efficacy of new medicines. The key is to focus on developing appropriate models and technologies that can accurately reflect human biology and physiology. This will require a collaborative effort among researchers, industry, and regulatory agencies to ensure that new drugs are safe and effective.