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 and, within this system, microdosing data are specifically accepted (11).

— *In silico:* At the other end of the scale, a computational approach, through the use of predictive *in silico* models built on real toxicological data, can be highly effective in identifying risk. There are now many systems that are commercially available (12), and evidence is emerging that these can provide early and accurate indications, not only about safety (13, 14), but also concerning efficacy issues (15–18). There is little doubt that such computational approaches will offer ever greater insights into potential efficacy and safety. The issue with *in silico* models is that they are only ever as good as the data on which they are based, and this would argue for an extension of human biology-based testing, both *in vivo* and *in vitro*.

— *In vitro:* An area that is particularly neglected is the evaluation of function in isolated human cells and tissues. The cell and tissue types available for such studies are theoretically unlimited, and the technologies that may be applied to them are extensive and ever-expanding. However, despite these attractions, relatively limited use is currently made of them, and the pharmaceutical industry shows little sign of moving further in this direction. There are a number of reasons for this apparent lack of enthusiasm, including: a) the difficulty in predicting activity, in the complex integrated system that is the human body, from studies on human isolated tissues; b) the absence of convincing evidence that human tissue-based methods are more reliable than the current animal-based tests; c) the current requirement of the regulatory authorities for animal-based data; and d) the lack of adequate access to the necessary tissues to support a human tissue-based strategy. While each of these objections is understandable, none is insuperable.

Extrapolation from *In Vitro* to *In Vivo*

In many cases, *in vitro* to *in vivo* extrapolation may not be as difficult as is supposed, and important advances have been made in this direction. In a recent paper, methods involving a combination of *in vitro* and *in silico* testing for the prediction of *in vivo* nausea and vomiting, have proved to be successful (19). Significant advances are also being made in the use of microfluidics, which allows quite complex systems to be constructed, encouraging the interaction of a range of contributory cell/tissue types in the investigation of drug metabolism (20, 21). This will undoubtedly be extended into measurements of function, facilitating the exploration and prediction, not only of clinical pharmacokinetic parameters, but also of pharmacodynamic parameters. Isolated cell types in co-culture or in tissue reconstructions can also provide useful insight into how a drug is likely to be handled *in vivo*. It is true that there will be physiological systems that prove resistant to modelling *in vitro*, and, in such cases, animal models may continue to be the most effective route forward. However, where this is the case, parallel human/animal *in vitro* tissue studies should be performed, to ensure that the chosen animal species will yield results that are as relevant as possible to humans.

Evidence that Human-based Tests Offer Any Advantages

While, in many cases, the demonstration of superior predictive power is lacking, this is arguably because there have been few proper comparative studies. The Safer Medicines Trust has been lobbying for such a study to be performed, and this has stimulated the drafting of *The Safety of Medicines* (Evaluation) Bill, advocating the performance of a proper systematic comparison. Although the original Bill was not afforded parliamentary time for debate in that session, it was relaunched as a *Ten Minute Rule* Bill — the *Safety of Medicines* Bill 2011, due for a second reading on the 22 October 2010 — and supported by *Early Day Motion 475, Safety of Medicines*. It remains to be seen whether this challenge will be taken up by the Department of Health and the pharmaceutical industry.

Availability of Necessary Tissues

Human tissues can be acquired for *bona fide* research purposes, and there are an increasing number of tissue banks from which these may be obtained. The tissues are almost exclusively acquired following therapeutic surgical removal or *post mortem,* at autopsy. While such samples are of considerable value, they do not supply what is required, if human tissue approaches are to successfully replace animal-based methods. The current retrieval procedures, surgical or *post mortem*, suffer from various limitations. For example:

— Only certain tissue types are removed surgically, thus many tissues can seldom, if ever, be obtained post-surgery.

— The tissue sample requirements of the pathologist, for record or diagnostic purposes, dictate that only small samples of tissue can be acquired by the surgical route.

— Tissue obtained post-surgery is usually diseased — that is why it is being removed. It is, therefore, virtually impossible to obtain true healthy control material by this means.

— Tissues obtained *post mortem*, while much wider in tissue type, are compromised in that there is inevitably a *post mortem* delay, which is seldom less than 12 hours and can often be 36–48 hours. Such tissues are physiologically compromised, and rarely in a viable condition, making them useless for functional studies.

— The bulk of *post mortem* tissue donors are elderly, and, as such, are unrepresentative of the patient population as a whole.

— Considering both retrieval procedures, and the low frequency and irregularity of the supply, these factors do not support the consistent availability that would be required to maintain a systematic human tissue-based test strategy.

Tissues from heart-beating donors: A possible solution

While the constraints represented by the sourcing of research tissue from surgery and *post mortem* seem highly limiting in terms of what can be achieved through the use of human tissue-based test methods, it need not be so. Such limitations could be minimised, or avoided completely, simply by mobilising an additional source of human tissue, namely, heart-beating (brainstem dead) organ donors. These donors are currently the primary source of organs for transplantation, but there seems to be no reason why any organs/tissues that are not required for transplant, could not be retrieved for research. Access to such material for research could potentially overcome all of the limitations associated with surgically-derived and *post mortem*-derived tissues. At present, access to such tissues is relatively infrequent and sporadic, and, while attempts have been made to improve access to this source of research tissue, they have had only limited success.

In 1999, an organisation was established to acquire and distribute donated human tissues for research, including those from heart-beating organ donors. This was the UK Human Tissue Bank (UKHTB). Ten years later, it closed its doors, partly through lack of support. The UKHTB's problem was that their rate of acquisition of many key human tissues for research proved inadequate to support the various potential users, meaning that human tissue-based programmes could take months to complete. As a result, researchers decided that human tissue studies could not constitute a key element in their discovery and development programmes, since speedy access to development-critical data is of critical importance. As interest in human tissue work declined, demand for the UKHTB's services declined with it. This is essentially a vicious circle of inadequate supply leading to decline in demand, and a lack of ability to invest in improving supply.

The fact is that, for human tissue work to succeed, it must be seen as 'need to have' rather than simply 'nice to have', and this will only come about if it becomes a regulatory requirement. But, because of its poor perception and its inadequate supply, little work is being undertaken to establish methodologies that could represent better means of establishing drug efficacy and safety. Therefore, the greatest immediate need is to ensure that tissue supply is adequate for the task. This could only be attained if the key stakeholders, namely the Department of Health, National Health Service Blood and Transplant (NHSBT), the pharmaceutical industry and the British public, were all convinced this is the way forward, and they were prepared to work together to achieve it.

The potential supply of human tissues by this route is considerable. In the 12 months to 31 March 2009, 3,513 organ transplants were performed, but this left a further 7,877 patients still on the waiting list (23). Significantly, the numbers of patients waiting for organ transplants is increasing year-on-year, and, by 3 September 2009, despite continuing transplantation, the number of those waiting had increased to 8,098 (23). The UK NHSBT is clearly not keeping up with demand. A plan needs to be devised that works to the benefit of all the stakeholders. A scheme to address the interests of all the stakeholders might take the following form:

— The National Health Service (NHS) commits to assisting the pharmaceutical industry to make more tissues available for research. It might do this by supporting existing tissue banks, and by requiring that the NHSBT is responsible for the recovery, not only of transplantable organs from heart-beating organ donors, but also of a wide range of other tissues, as required by the research community.

— Consent for research use will have to be assured for all retrieved tissues. This requires that the public are educated as to the value, and indeed, the necessity, of this source of tissue for securing the future of pharmaceutical research.

— The pharmaceutical industry must pledge to support this initiative, either through direct grants to the NHSBT and/or by funding the NHSBT, such that the NHSBT receives industry funding at a level that covers the true cost of tissue recovery, including the support of

enhanced recovery teams and the infrastructure required to coordinate retrieval, storage and distribution.

— The Government and the NHS will have the necessary role of educating the public as to the importance of their participation, as their consent will be a key element. Fortunately, following the demise of UKHTB, the resource that it represented is now being provided by another organisation, and it is hoped that access to, and hence interest in, human tissues for research will ensure the viability of this operation (24).

Conclusions

The benefits to the various stakeholders of increased heart-beating organ and tissue donation can be summarised as follows:

— *Researchers:* Access to adequate supplies of human materials, necessary to enable human-based efficacy and safety tests to be developed, and for the furtherance of drug discovery and development.

— *Department of Health and NHSBT:* Input from the pharmaceutical industry community to support organ/tissue recovery services, increasing their capacity to perform their primary responsibility of organ and tissue transplantation.

— *Pharmaceutical industry:* Improved access to human biological test methods, resulting in an increased capability to develop and market safe and effective new medicines, and a concomitant reduction in the financial and public relation costs associated with conducting work on animals.

— *Public:* An increase in the numbers of transplants performed, increased delivery of safe, effective and affordable new medicines, and a decrease in the numbers of experimental animals used by the pharmaceutical industry.

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