From Bench to FDA: Validation of In Vitro Methods of Prediction of Human Toxicity

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Why is species-relevant testing important:

- More than 2 million Americans received emergency hospital treatment in 2009 for an adverse reaction to a prescribed medication.
- Adverse drug reactions kill 197,000 EU citizens/year, at a cost of €79 billion, according to the European Commission in 2008.
- 92% of experimental new drugs fail in clinical trials, despite appearing to be safe and effective in pre-clinical tests.
- A recent European study revealed that reducing the level of regulatory pre-clinical safety testing had no effect on incidence of use-limiting side effects.
- There seems to be an inherent illogicality in using one species to predict drug activities in another, unrelated species.
- This is a particular problem with the testing of biologicals, where drugs are specifically targeted to human proteins.

Abstract

Safer Medicines Trust is a UK-based charity whose mission is to improve patient safety by encouraging an increased focus on human-based test methods in the regulatory approval process. We believe that one key obstacle to the introduction of novel human-based approaches to drug safety assessment is the lack of confidence in the ability of such approaches to provide data that are the equal of or even superior to those currently required by the regulatory authorities. In order to address this, Safer Medicines Trust has designed a small, focused study involving a selection of failed marketed drugs (each with a matched negative control) and a range of state-of-the-art human-based *in vitro* tests, to indicate whether such tests can identify safety issues missed by the currently-required animal-based test methods. We believe that this study represents a novel and potentially highly valuable approach to addressing this important question. Suggestions for additional novel human-based test methods and suitable compound pairs for inclusion in the study, and means by which to engage the pharmaceutical industry and the regulatory authorities will be welcomed.

Introduction

Clearly, our currently accepted pre-clinical tests are far from perfect and need to be improved. Many advances in predictive toxicology offer the potential to increase safety, with the added bonus of reducing both the time and cost of drug development. But are they sufficiently validated to be accepted in the industry and by the regulatory authorities who are responsible for ensuring patient safety?

While there are several important studies underway to investigate the value of novel approaches, these are mostly large multi-centre trials. While necessary to conduct, they are unlikely to produce a clear outcome for some years. In the meantime, pharmaceutical companies will continue to test their products in line with the current regulatory guidelines, and any serious attempts to move towards more human-based testing are likely to be minimal.

We therefore propose a small study to compare new human *in vitro* approaches with the current regime of regulatory tests in order to bring the possible advantages of such approaches to the attention of both pharmaceutical developers and the regulatory authorities.

To date, there has been no controlled study to establish the merits of a range of novel approaches relative to the current approach.

Pilot study overview

We have selected six drugs (more may be added) that passed the pre-clinical safety hurdles and obtained approval for clinical use but were withdrawn subsequent to causing serious adverse effects in patients (Table 1). In order to adequately control the study, each 'failed' drug is paired with a chemically and/or functionally similar drug that does not share its specific toxicity. All 12 drugs will be submitted, blinded, to a range of promising commercially available human biology-based tests (Table 2).

Toxic Compound	Negative Matched Control
QT interval prolongation, arrhythmias	No side effects noted
Mitochondrial damage, rhabdomyolysis, myopathy, hepatotoxicity	Mild muscle cramps, rare abnormal liver tests
Heart valve defects	No side effects noted
Heart attacks	No side effects noted
Kidney damage, hemolytic anaemia	Rare: Tendon ruptures, tendonitis, liver failure, hERG blockade
Hepatotoxicity	Rare: Abnormal liver and heart tests

Table 1. Mechanisms of toxicity of study compounds

More than 40 companies offer a wide range of relevant *in vitro* technologies. We have selected 8 (more may be added) that fulfil the following criteria: scientific validity of the test, demonstrated by at least one published external validation study; commercial availability; practical throughput and reasonable cost. For this pilot study we focus primarily on toxicities affecting heart, liver, kidney and muscle tissue, which are the major toxicities that cause failure of drugs in humans.

Company	Human *in vitro* technology
Axiogenesis	Cor 4U® human induced pluripotent stem cell (IPS)-derived cardiomyocyte product line for use in testing the efficacy and safety of potential drugs
Biopta	Human *in vitro* resistance vessel vasoconstriction and vasodilation assays
BioSeek	BioMAP® systems incorporate predictive primary human cell-based disease models that generate uniquely informative biological activity profiles for potential drugs
CeeTox	*In vitro* toxicity screening assays for drug discovery, including: Acute Toxicity Screen; Drug-drug Interaction Tox Screen; CardioTox Panel®
Cerep	*In vitro* screening and profiling using proprietary database BioPrint® to model clinical effects of drugs from their molecular properties
Cyprotex	*In vitro* toxicity prediction using HepG2 cell line and 10-parameter high content imaging platform
GE Healthcare	Drug screening tests using cells derived from human embryonic stem cells
InSphero	3-D human primary microtissues

Table 2. Technologies to be tested in the study

The study will be overseen by an independent expert panel and all data and analysis will be published promptly and in full on completion.

While this study will be on a much smaller scale than such initiatives as ToxCast and Tox21, it will be considerably simpler, more focused, less expensive and will deliver results in a much shorter time-frame. We feel that such studies will boost interest in and support for the larger studies and encourage interim regulatory changes long before the conclusion of the large-scale studies.

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