Putting patient safety first Registered Charity 1039411
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Proposal to humanise drug safety testing

Why? Despite international efforts to stem attrition, the failure in clinical trials of drug candidates that appeared safe and effective in preclinical testing remains at an unsustainable 92%. Adverse drug reactions kill 197,000 people annually in the EU and upwards of 100,000 in the US and are increasing still further. A transformation in the predictive ability of preclinical tests is needed urgently.

A new generation of more physiologically relevant and predictive toxicological tools, using human cells and tissues, is now available – but no paradigm shift has occurred. Many of these tools are being evaluated through important large-scale initiatives such as Tox21, ToxCast, IMI, EU-NETVAL and SEURAT, which will be game-changing but will not be concluded for many years. Meanwhile, since the need for change is urgent, we propose a method to identify a more reliable testing regime more rapidly, through a process of '**comparative validation**'.

Comparative trials are the life-blood of science and medicine. Only by comparing different approaches can we move towards the system that proves more effective.

How? To date, there has been no controlled study to compare the performance of the current (mainly animal-based) test regime relative to an approach based on human biology *in vitro*, *in silico* and *in vivo*, despite numerous examples of such techniques predicting toxicities that were missed by the current regime.

Safer Medicines Trust has designed a pilot study to compare the predictive value of the two approaches. A selection of drugs withdrawn from the market in recent years, due to unexpected severe toxicities in patients, will be subjected to a range of human-focused tests to see if any or all of them can identify the toxicities that led to each withdrawal. Crucially, each toxic drug will be paired with a related 'clean' compound to serve as a negative control, giving the study more rigour.

The study is relatively inexpensive and could be completed within 12 months. Because the study will be blinded, its prospective focus will be only on *in vitro* methods, while *in silico* and *in vivo* data will be integrated retrospectively in the study's analysis. This study will demonstrate – for the first time – whether a combination of human-focused tests could perform better than the regime that is currently in place. If so, improvements could be made to the existing regime immediately, with further refinements being made incrementally: a process employed successfully in all other aspects of technology development.

The technologies to be tested are already commercially available and possess a significant level of validation. They employ a variety of high content screens, allowing detection of multiple mechanisms of toxicity that were not possible to detect 20 or even 5 years ago. Every technology-providing company we have selected endorses the proposed study and has agreed to participate at cost.

We invite a consortium of pharmaceutical companies and non-profit organisations to fund the study. Companies are encouraged, but not required, to submit their own proprietary compounds in addition to the ones we recommend for the study. Our only requirements are that the compounds are handled independently and that on completion of the study, all results are reported promptly in a peer-reviewed publication, according to open access and creative commons principles.