



Opportunities for use of one species for longer-term toxicology testing during drug development: a cross-industry evaluation

What is the background to the project?

It has been common practice for more than 40 years to perform toxicity tests on pharmaceutical drugs in two animal species (a rodent and a non-rodent) for conventional drugs (e.g. “small molecules”). This principle is also included within international regulatory guidelines for pharmaceuticals (e.g. [ICH M3 guidelines](#)). In more recent years, many new and different types of molecules have been developed as drugs (e.g. “biologicals”), the testing of which is also covered by international guidelines (e.g. [ICH S6 guidelines](#)). Because of the nature of biological drugs, there is often scientific justification for the use of one animal species only for testing – either for the whole testing “package” or for the studies that are conducted later in the drug development programme. The aim of our collaboration was to explore whether these opportunities to use one species only could also be safely applied to a wider range of drugs, including small molecules.

What does the paper report?

[The paper](#), published in *Regulatory Toxicology and Pharmacology*, reports the outcomes from an NC3Rs-led project that involved a collaboration with 30 companies and regulatory bodies from around the world. The project was co-funded by an industry consortium led by the Association of the British Pharmaceutical Industry¹.

The collaboration was formed to investigate the use of two species – a rodent such as mice or rats, and a non-rodent such as dogs, minipigs or monkeys – in toxicity studies that are performed to provide information on the safety of potential new medicines before human clinical trials.

The question we investigated was whether it would be possible to use data from one species only without compromising human safety. This is an important project as the findings could have a big impact on the number of animals used. Although the precise number of animals used per drug varies depending on a range of factors, many thousands of animals are used worldwide for toxicity testing each year.

¹ The following companies provided funding to the NC3Rs as part of the ABPI-NC3Rs collaboration: AstraZeneca, Charles River Laboratories Ltd, Covance Laboratories, Envigo, GlaxoSmithKline and UCB Pharma.

To answer this question, we analysed detailed data on the toxicity testing of 172 compounds provided by 18 companies. The results indicate:

- **For biological drugs:** There are opportunities for companies to use a single species only for more biological drugs particularly for the later stage toxicity studies (e.g. those studies of 13 to 39-week duration) within the existing regulations.
- **For small molecule drugs:** There is preliminary evidence that one species only could be used for some toxicity tests for these drugs. However, there is a need to build a more substantive evidence base to define when the use of one species is (or is not) appropriate.

Who was involved in this research?

This is a complex project and we established an international Working Group consisting of 37 representatives from 30 companies and regulators to make sure that we could access the data we needed and had the right expertise for the detailed analysis required.

The pharmaceutical companies or contract research organisations that participated were: ApconiX, AstraZeneca, Bayer Pharma, Celgene, Charles River Laboratories, Chugai Pharma, Covance, Cytokinetics, Eisai Inc, Eli Lilly, Envigo, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Sequani, Servier, Takeda Pharmaceuticals, Teva Pharmaceuticals, UCB and VAST Pharma Solutions.

We also had representation from: the Belgian Federal Agency for Medicines and Health Products (FAMHP), US Food and Drug Administration (FDA) and UK Medicines and Healthcare products Regulatory Agency (MHRA) regulatory authorities.

What have other investigations shown?

The use of animals in toxicity testing is an area where there is a lot of activity nationally and internationally to find alternatives and minimise animal suffering. The NC3Rs has a large programme of work in this area.

To our knowledge, this is the first research into whether a single animal species could be used more often for 13 to 39-week toxicity studies. Other groups have looked at the need for testing in two species, but these have focused on whether the findings seen in animals are predictive of what happens when a drug is given to humans, and whether the use of one or two species improves the predictions. These studies have used animal toxicity data for already marketed drugs, and although interesting, have limitations as they miss the data for drugs that were stopped, or as yet unmarketed.

Are the findings from the NC3Rs investigation different to what has been shown by others?

Most other work in this area has focused on whether animal studies predict what will happen in humans. This was not the focus of our investigation and therefore it is not possible to compare our findings with those of others.

How will the report affect the use of dogs and monkeys?

The NC3Rs remit includes all animals that are used in scientific research from fish to mice, to dogs and monkeys. We understand that many people are particularly concerned about the use of so-called higher species like monkeys and dogs.

For biological drugs: Monkeys are often the most relevant non-rodent species for toxicity testing of biologicals, but rats are often used too. The current regulations outline the circumstances where one species only can be used and our data reinforce this, highlighting where there are opportunities to use rats only instead of monkeys in the later stage toxicity studies.

Small molecule drugs: Dogs are frequently the non-rodent species used for toxicity testing of small molecules, along with rats or mice. Our data shows that there might be more opportunities to avoid the use of the dog, but additional data is required to support any recommendations to changes to current approaches and regulatory guidelines. It is likely that the number of dogs used will not change at least in the short-term. However, pharmaceutical companies have the option of discussing the design of the later-stage toxicity studies with regulators and the findings of the collaboration will raise the profile of opportunities for testing in a rodent species only.

How many dogs and monkeys are used in toxicology testing each year?

It is difficult to estimate how many monkeys and dogs are used for the toxicity testing of pharmaceuticals globally. Many countries do not provide information. In the UK, the number of animals used in scientific procedures is provided annually by the Home Office. Although the UK [figures](#) do specify the number and species of animals used and the type of research and testing, they are not specific for the pharmaceutical toxicity tests we have been investigating.

What will the NC3Rs do next in this area?

We are currently preparing publications to explore other aspects of the dataset we have collected, including the criteria which are used by companies to select which animal species to use. We are also funding research that in the long-term will lead to cell tissue and computer models replacing the use of animals for toxicity testing.