

# NC3Rs/ABPI collaborative strategy for challenging the use of non-human primates in drug discovery and development

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## Background

The largest use of non-human primates (hereinafter primates) in the UK is in the assessment of pharmaceutical safety and efficacy. The use of primates in regulatory toxicology has recently been reviewed by the APC and a number of recommendations have been made, however there has yet to be a comprehensive scientific review of the rationale for this use and 3Rs opportunities across all areas of use in drug discovery and development. Such a project also has the potential to support the science and enhance decision making in drug development. With the use of primates potentially increasing in some areas, it is timely to assess the necessity and value of primate use and scope for the 3Rs.

In partnership with the Association of the British Pharmaceutical Industry (ABPI), the NC3Rs has developed a strategy to examine and review the rationale for the use of primates in drug discovery and development, with the aim of minimising their use and enhancing the implementation of the 3Rs. Four areas, namely drug dependency studies, biologicals, pharmacokinetics and regulatory toxicology, have been identified as priorities for consideration as a result of detailed discussions with ABPI member companies. Under the umbrella of an expert steering group, four working groups have been established to consider primate use in each of these areas, focussing on (i) scientific rationale for use and potential replacement and reduction strategies, (ii) regulatory pressure for use, (iii) obstacles to implementing the 3R, and (iv) harmonisation and refinement of study designs.

The work of the four groups will be reported through various avenues including:

- ABPI and European Federation of Pharmaceutical Industries (EFPIA)
- direct feedback to individual companies
- publications in peer reviewed journals
- presentation to learned societies e.g. British Toxicology Society
- output to the public audience including articles on the NC3Rs website

## Working Groups

### Preclinical abuse liability studies

**Proposal:** There are novel opportunities to apply the 3Rs to primate use in drug dependency and abuse liability studies.

Dependency is an adverse drug reaction that can occur with some drugs that act on the central nervous system, for example anti-depressants. The occurrence of this adverse event in humans is predicted by preclinical studies in animals. The hypothesis to be examined by this working group is that rodent models of drug dependency used in preclinical studies are predictive of abuse potential in humans and there is not sufficient added value to be obtained from using primates in these studies. The working group will analyse data from rodent models of abuse potential to determine if rodents are sufficiently predictive of drug dependency. Assuming this hypothesis is scientifically proven, there are still international and regulatory limitations to the global acceptance of the rodent as a suitable model. To prepare for this challenge the working group consists of eminent international scientists from academia, industry and the regulatory agencies.

### Development of biologicals e.g. monoclonal antibodies, vaccines

**Proposal:** There is opportunity to reassess primate use in the development of biologicals.

Biologicals or biotechnology derived products are extremely diverse and include monoclonal antibodies, and large therapeutic proteins such as hormones, cytokines and enzymes. Their use as pharmaceutical products is increasing because biologicals are extremely specific to their target; one advantage of this is minimised toxicity. However, this high specificity limits species suitability for safety studies; for example, a

monoclonal antibody may only cross-react with its primate counterpart and may initiate an immune response in species other than the primate. To identify the best opportunities to reduce and replace primate use the NC3Rs is hosting a one-day workshop to map out what the process of drug discovery and development would look like for biologicals if primates could not be used. Initially this will be an academic/hypothetical exercise with emphasis on pharmacokinetics, drug development and toxicology. The ideas from the workshop will be taken forward by an expert working group which includes large pharmaceutical companies, biotechnology companies, contract research organisations and the regulatory agencies.

### **Pharmacokinetics**

**Proposal:** The implementation of the 3Rs in pharmacokinetics could be enhanced.

The pharmacokinetic profile of a drug is used by the pharmaceutical industry to select suitable new drug candidates and to predict drug metabolism in man for safety pharmacology. For example, if a chemical is likely to be metabolised very quickly it can be impractical to administer an effective dose. The hypothesis is that the use of *in vitro* technologies in combination with rodent data may be sufficient to predict human pharmacokinetics. The working group will review data to assess (i) whether primates are the most valid predictive species in pharmacokinetic studies and (ii) whether their use as a second species increases prediction and extrapolation to man. There have been a number of publications on this topic within individual companies but an inter-company data comparison would be informative to distinguish between requirement and routine.

### **Regulatory toxicology**

**Proposal:** There is scope to review the justification for using primates in toxicity studies.

Toxicology testing normally requires data from two species, one rodent, usually the rat, and one non-rodent. Primates are often used as the second species in toxicity tests. There are no regulatory guidelines that specifically require the use of primates and there is scope to review the scientific rationale for their use. Part of this review will involve an investigation of the two species approach to toxicology and reassessment of toxicology practice which has remained unchanged over many years. The working group will assess the challenge of avoiding the use of primates at the expense of other species, for example the dog, and take into account the APC recommendations detailed in its report on the use of primates in regulatory toxicology.