# Non-Rodent Selection in Pharmaceutical Toxicology

A ‘Points to Consider’ document, developed by the ABPI in conjunction with the UK Home Office

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# Contents

## 1. Introduction

The selection of the appropriate non-rodent species in pharmaceutical toxicology has long been a major topic of discussion between the industry, the product regulatory agencies (i.e. the MCA/Department of Health in the UK) and the national authorities responsible for animal welfare (the Home Office). In the UK, various discussions have been held with the Home Office on the relative benefits of, and scientific justification for, various species (the dog, marmoset etc) and the ABPI was instrumental in the review of the marmoset in preclinical toxicology (Smith *et al* 2000). Studies coordinated, for example, by the International Life Sciences Institute (ILSI) on the concordance of the toxicity of pharmaceuticals in humans and in animals (Olson *et al* 2000) have sought to assess the relevance of *in vivo* models that are predictive for adverse effects in humans exposed to chemicals, paying attention (in this case) to the value of dog studies. At the same time, industry has recognised society's concern over the use of the dog in research and is working with welfare organisations to try and minimise dog use in preclinical safety evaluation (Smith *et al* 2002).

Against this background, the ABPI and its PreClinical Drug Safety Advisory Group organised an informal discussion meeting some months ago to review the current practices used by industry in its selection of non-rodent species in pharmaceutical toxicology. Some of the issues arising from that meeting are summarised in this discussion paper. The paper, which has been developed following dialogue with the UK Home Office, should help toxicologists ensure that they are working to current good practices. It will hopefully stimulate further discussions across the sector on how improvements can be made in the selection of the appropriate second species. Both new applicants and ethical review groups can also use it during the authoring and reviewing of Project Licences.

## 2. Background

Pharmaceuticals must be tested in rodents and non-rodents (except in exceptional circumstances) before and also throughout the clinical phases of drug development programmes to help assure their safe use in humans. This discussion paper examines the selection of the non-rodent for repeat dose general toxicology studies with small molecule compounds. The non-rodent most generally used at present is the dog, although sometimes a monkey (the cynomolgus macaque or marmoset), a pig (often a miniature breed) or, rarely, the ferret is selected. The selection is based on regulatory requirements, ethics, the scientific requirement to obtain the best possible prediction of the human response and animal husbandry and a number of technical issues.

Because the decision is often a complex one and will evolve with more knowledge, it is important to regularly review the factors that have to be taken into account.

# 3. Criteria currently used in species selection

## 3.1 Regulatory requirements

Regulatory requirements include both those aspects of the Animals (Scientific Procedures) Act 1986, and the regulation of the safety, quality and efficacy of medicinal products.

### 3.1.1 Requirements of the Animals (Scientific Procedures) Act 1986

- Minimise the suffering caused by using animals that have the lowest neurophysiological sensitivity (that is to say, have the least capacity to experience pain, distress or lasting harm)
- Not use cats, dogs, equidae or non-human primates unless animals of no other species are suitable or it is not practicable to obtain animals of any other species that are suitable
- Any use of non-human primates must be specifically justified. Authority to use primates should be sought only when no other species would be suitable. Only captive-bred primates may be used, with rare exceptions. Use of Old-World rather than New-World primates must also be justified.

### 3.1.2 Requirements of product safety regulators

These are addressed in:

Council Directive 2001/83/EC

CPMP/ICH 286/95 adopted 1997 and modified November 2000 (Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals).

- Safety tests in 2 species of mammals, one a non-rodent, unless only 1 species is relevant
- Species chosen based on similarity to humans where known with regard to pharmacokinetic profile, including biotransformation and conversion of pro-drug to active substance
- Wherever possible, selected species should respond to the primary pharmacodynamic effect of the substance

There is often a conflict between the requirements of the product safety legislation, which implies that species selection be based on similarity to humans (hence higher species), and that of animal welfare legislation, which requires that 'lower' species must be used. It is essential therefore to have effective dialogue between the industry, Home Office and the Department of Health/Medicines Control Agency.

It is often beneficial, and sometime critical, to discuss species selection with the relevant regulatory authority before embarking on a non-standard programme of work, or one involving the use of a species other than the dog or primate. The lack of experience (and hence acceptance) of a species by Health Departments can be a cause of major problems in some cases.

## 3.2 Ethical requirements

The Ethical Review Process (ERP) remains the primary issue here enabling individual researchers to develop their own ethical criteria.

- It may be quicker and may require fewer animals to default to a well characterised species than to use a less familiar species, but this is acknowledged as a pressure on always maintaining the *status quo*
- Neurophysiological sensitivity is unclear and contradictory

  – is the dog more sensitive than the pig, for example?

Some of these issues have recently been addressed by UFAW in its Symposium on Consciousness and should be noted by researchers/Home Office (Hubrecht, 2001).

- The industry acknowledges that the perception of the public may have an impact on regulatory pressures affecting species use, as in the case of the dog.

- In the early stages of developing a drug, the amount of the new drug that can be made is often very small. If this lack of drug directly slows the development of a new drug for a serious medical condition that currently has no treatment, then the size of the animal becomes important as less drug is needed to test for safety. An example of the ethical issue that then arises is the use of a 400 gram marmoset monkey compared to a 15 kilogram dog.

## 3.3 Scientific requirements

There are numerous examples of scientific criteria that need to be taken into account:

### 3.3.1 Those specific to the substance under study

- Similarity to human toxicity or ADME profile for that substance, based on *in vitro* data and/or related compounds already given to humans

- Similarity to the human of an aspect of anatomy or physiology which is likely to be relevant to the pharmacological or toxic response to the compound. Such theoretical considerations must, however, be based on good experimental science, which must be well planned, properly conducted and appropriately analysed

- Previous toxicological experience with compounds of that class showing good correlation with human studies

- Presence of the required pharmacodynamic response (although this is not absolutely necessary. Regulatory authorities usually want one of the test species to be responsive, and that could be the rodent)

- Previous use of the species as an efficacy model

  – May allow easier dose selection

  – May help predict toxicity if this is related to the pharmacology of the compound

- Absence of immune response against the substance (most relevant for biotechnology products)

- Information from other studies during the development of the compound (animal or human) which may indicate that an additional species is needed to investigate a toxic effect or the effects of a significant metabolite of humans which is not formed in the original non-rodent species. Where possible, other species should be tested in the early stages of drug development, to help select the best species for the later stages

- Ability to achieve required exposure (although this seldom determines species selection) but might determine an inappropriate species

*Dilemma*: we need to know the human response to select the closest species, but we need animal data to know the human response

### 3.3.2 Those that are generic (i.e. relevant to any substance)

These are far less robust than substance-specific justifications but some examples are:

- Historical predictivity

  – e.g. analyses of the ILSI-type

- Phylogenetic status in relation to humans

- Similarity to human of important metabolic/biochemical processes

  – e.g. CYP450 structures or activities

- Availability of background data, which is especially important to help distinguish treatment-related pathological effects from spontaneous findings

### 3.4 Additional technical/animal welfare aspects of the use of various species

There are a number of additional factors that need to be taken into account in the choice of species. Some of the factors listed below are either scientific criteria, e.g. the outcome of species specific responses, or are additional other animal welfare issues which should be included in any ERP review.

- One must be aware of atypical species responses (i.e. Cremaphor in dogs) which might cause unnecessary suffering. Work should only be performed within the limitations of the project licence and where the effects of administration are not expected to exceed the defined severity limits
- Availability, especially without prolonged transport or prolonged lead time for breeding/supply (of mature animals)
- Husbandry, including ability to provide a rich environment, effect on the animals of experimental procedures. Experimenters must be willing to try new methods of husbandry where this would be valuable
- Ease of conducting procedures (e.g. dosing, taking samples)
- Interpretation of data and experience of scientists
- Use of a smaller species may increase the number of animals needed per experiment, due to blood sampling limitations
- Age at sexual maturity: it can be difficult to use slower maturing species, yet the ideal is to do the work in mature animals, to provide maximum predictivity for adult humans

### 3.5 Summary of current selection practice in the UK

Judgement has to be used during the selection process, but it should be based on the most up to date information available. For the safety assessment programme, early *in vitro* and *in vivo* DMPK studies (possibly including *in vivo* work in several species to supply comparative information) is used to help select the species. In most cases, the dog is effectively the default species, driven by historical data/ experience, practicalities, legislative requirements and availability. Primates, however, are also used where dogs would not be suitable, and some 'lower' non-rodent species e.g. the pig, are also sometimes used. Non-rodents are rarely used for screening studies unless driven by previous experience, e.g. the pharmacological receptor is only present in a particular species or previous experience has shown the rodent as non-predictive for a specific toxicity within a particular drug class.

The rabbit is usually accepted by product safety regulators as a suitable non-rodent species only in cases where it has been shown to resemble humans and the dog and primate have been shown not to do so.

There is currently little switching of non-rodent species during development of a new chemical entity although a second non-rodent is sometimes used in addition to the first to clarify particular points, particularly in the light of information from human trials.

## 4. Identification of necessary long term objectives on species selection

As this paper has shown, the pharmaceutical industry often uses species such as the dog in regulatory toxicology studies because it has always done so, and other species are not used as much because they are less accepted by regulators. As a result, extensive knowledge and understanding around the use of the dog does exist, especially within companies. But, it is clear that more background work is needed to characterise other species, which will in itself involve additional animal use. As this matter goes forward the importance of getting the cost/benefit equation sorted cannot be overestimated. What does the use of each species offer in respect of animal welfare and the ability to assure patient safety? It is not just the industry's responsibility to progress this matter; this needs to be shared with consumers, health authorities, the government and animal welfare groups.

The identification of the most relevant animal species for the safety evaluation of a new medicinal product is, of course, an international undertaking. There does need to be improved liaison between the product safety regulators (at the UK, European and International level) with animal welfare regulators to justify a broader range of species and to explore ways of sharing data.

The ABPI has identified a number of other considerations in the selection of species that are anticipated in the shorter term, or would be theoretically desirable in the longer term. These include the need for:

- Improvements in scientific knowledge to enable us to select the best species. In particular, better pharmacological study of gene/receptor/enzyme target and associated likely effects is needed before embarking on toxicology
- A wider selection of species should be screened (*in vitro* metabolism, receptor binding) during drug discovery/early development to enable the selection of the best/most appropriate species in terms of similarity of biological/toxic response to humans
- Although the industry already carries out much research into the development of 'alternatives', further work done on the identification and validation of other species would give researchers a wider choice
- Toxicogenomics/toxicoproteomics may provide useful information on toxicological mechanisms and how these differ between species
- More uniform application of the principles of metabolic and pharmacodynamic profiles in the selection of species for toxicology programmes is needed. Systematic confirmation that the metabolic profile obtained in man has been evaluated in the preclinical species used for the toxicology programme is needed
- Transgenic rodent species, engineered to resemble humans in some responses could be valuable in some toxicological work and could, in some cases, replace higher species. The use of transgenic animals, however, does pose some ethical issues and there is a need for those developing such experimental models to be responsive to these concerns. Many of these issues have been discussed at length in the Animal Procedures Committee report on biotechnology
- Further data sharing on issues such as class effects could help species selection if this could be done without compromising commercial interests or intellectual property requirements.
- Use of specific Safety Pharmacology data with close attention to functional change can help to define species responses and thus aid selection in some cases.
- Identification of surrogate endpoints or biomarkers for particular mechanisms of

toxicity will aid species selection and give opportunities to track changes seen in animals to those seen in man. Such surrogate endpoints may also give information on the dynamic range of any response and therefore give information on species sensitivity in comparison to man

- Earlier studies in humans would establish ADME criteria, which would help select the most predictive non-rodent species in terms of metabolism and kinetic criteria

- There is a general need to compile more information internationally on the value of non-rodent (and rodent) toxicology, both in early and longer clinical trials

- The industry needs to be able to search its data for effects of chemically related or pharmacologically similar compounds and evolve better *in silico* tools to predict parameters relevant to species selections

## 5. Supply and demand of non-rodent species

Because of the long lead-in time to develop a viable production colony of any non-rodent, it is not surprising that in the UK this choice is limited to the dog and marmoset. There is no sustainable supply of ferrets and the only breeder of minipigs is based in mainland Europe. Old World primates are only available from breeders outside Europe.

This limitation of supply, together with the ensuing welfare issues associated with transport, mean that the dog and marmoset remain the species of choice in the UK. However, there is continued pressure on these species, as a result of judicial review brought about by the BUAV. It is important that scientists continue to provide robust justification for the selection of their non-rodent using the most up to date scientific and animal welfare based arguments to counteract this pressure.

## 6. References


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