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GOOD PRACTICE GUIDELINES

The Selection of Non-rodent species for Pharmaceutical Toxicology

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THE SELECTION OF NON-RODENT SPECIES FOR PHARMACEUTICAL TOXICOLOGY

Background

Ensuring human safety in clinical trials and when medicines are on the market requires testing in two mammalian species, one of which is normally expected to be a non-rodent (note for guidance CPMP/ICH/286/95). Selecting the correct non-rodent is very important as it will maximise human safety, clinical benefit and animal welfare. Several factors constrain the toxicologist in making this selection, however, including inadequate scientific information at the stage when the selection has to be made, experience with and availability of the full range of species and the need to balance scientific, ethical and legal constraints. There is a regulatory difference in emphasis between requirements since animal welfare laws (EU Directive 86/609/EEC) require that animals of a lower neuropsychological sensitivity must be proved unsuitable before higher species are used whilst safety regulators require that species selection be based on similarity to humans. Additionally, within the LJK, further justification is required before dogs, cats, equidae or non-human primates can be used (Animals (Scientific Procedures) Act 1986).

Current Selection Criteria

The selection will be made using a combination of ethical. scientific and practical considerations to obtain the best possible prediction of human response:-

Ethical Considerations

The species selected should have the lowest welfare cost as a result of experimentation including transport to the laboratory, captivity, handling and experimental procedures. For example, there is no evidence that the minipig has less capacity to experience pain, distress or lasting harm than the dog in this situation. Similarly it is difficult to find evidence that the marmoset, when purpose bred and group housed in an enriched environment, suffers more than the dog. This ethical judgement between companies and countries may be different and can be influenced by public opinion. Finally, the human ethical argument needs to be considered. For example, an ethical argument can be made to use smaller species (marmoset), even though it is a primate, where its use will significantly accelerate drug development (the use of the marmoset may accelerate drug development by up to 18 months when compound synthesis is slow so that sufficient compound is not available to test using larger animals).

Scientifíc Considerations

The target receptor should be present in the test species and the species should demonstrate appropriate pharmacodynamic response. The drug should have adequate bioavailability and comparative metabolic profile with systemic exposure exceeding that in humans (where achievable). If the clinical route of administration cannot be used it is important that both the distribution and pattern of drug elimination are similar. There should be adequate background data in the species to allow

interpretation of findings, particularly those associated with histopathology. Generic justifications include the phylogenetic status in relation to humans and the similarity of important physiological processes such as cytochrome P450 mediated metabolism.

Practical Considerations

The species chosen should be practical in terms of availability, transportation to the laboratory, husbandry, cost, ability to perform procedures and assess adverse effects and compound requirements. The use of a smaller species may increase the number of animals needed per experiment due to blood sampling limitations.

The Selection Process

There will frequently not be a clear-cut option for the choice of species, especially in early development when there is inadequate information. The principle of choosing a species on a case-by-case basis should be adopted and early in vitro and in vivo DMPK work (possibly in several species) should be used to help the selection. However, the dog is the primary non-rodent species in toxicology because of historical data/experience, practicalities, legislative requirements and availability. Primates should only be used where dogs are unsuitable and the marmoset has been and will likely be adopted as an additional non-rodent species to the dog where appropriate. It should be considered before using an Old World Primate (Macaque). Individual projects may have scientific reasons for using the minipig and this should be considered before using a non-human primate. The ferret is unlikely to be used in the near future.

The following attached table and decision tree should be used when justifying the use of the non-rodent species both internally and at Contract Research Organisations.

Table 1

Comparison of Suitability of Non-rodent Species

	Macaque	**Marmoset**	**Dog**	**Ferret**	**Minipig**
Sensitivity to experimentation /captivity	A primate and not domesticated	A primate And not domesticated	Tolerant of captivity and proper handling	Not fully domesticated	
Availability	Poor	Moderately good	Moderately good	Poor, but in accord with low demand and could probably increase	Poor, but in accord with low demand and could probably increase
Flexibility of supply (generation time, number per litter)	Poor	Poor	Moderately good	Good	Moderately good
Ease of transport to laboratory	Difficult	Most from UK – some 'in house'	Most from UK	Small animals and probably from UK	Generally from Denmark, all pigs prone to heat-stress
Ease of housing	Difficult (space, environmental needs)	Lower minimum space requirements than macaques	Requirements for space, exercise	Need to control sexual activity	Requires space
Ease of correct feeding	Well established	Need to ensure Vit D_3 intake can create problems	Well established	Some dislike lab food	Well established
Ease of handling	Eases with training of animal	Can present problems	Needs time and care though domesticated	Eases with training of animal	Can present problems

continued……

Comparison of Suitability of Non-rodent Species continued …..

continued…	Macaque	Marmoset	Dog	Ferret	Minipig
Ease of dosing	No special problems	Moderately difficult	Well established	Moderately difficult	Moderately difficult
Ease of sampling	No special problems	Moderately difficult	No special problems	Difficult	Moderately difficult
Amount of experience with species in tox	Moderate	Little / moderate	Much	Little	Little
Variability/ spontaneous pathology	Small, but interpretation requires experienced pathologist	Small, but interpretation requires experienced pathologist	Small	Large due to sex differences	Moderate
Similarity to human	Probably high	Probably fairly high	Probably moderate	Probably moderate	Probably moderate
Body weight (kg)	4-6	0.4	12	0.6-2	10 – 35
Health	Care needed with zoonoses	Can be problems with infections and Vit D_3 deficiency	Good	Can be problems with infections	Can be problems with infections
Suitability for repro studies	Poor	Moderately poor	Poor	Moderately good	Moderately good

Decision Tree to Aid Selection (based on 86/609EU)