Animal models

Introduction

For all types of medicines and clinical trials in the medicine development process, the use of relevant non-clinical models and animal species is fundamental in obtaining predictive data for humans. For most new medicines, this is achieved by applying science-driven strategies. This is especially true when studying biologically derived medicines. Therefore much effort goes into the selection of the most predictive testing systems and the most predictive animal species.

Selecting an animal model

The selection of an animal species is based on the similarities between the animal species and humans in aspects such as:

- pharmacodynamics (safety pharmacology)
- pharmacokinetics, and
- physiology and pathophysiology

The pharmacodynamics (the action of the medicines on the body) in the animal species should be comparable to humans. The target, structural homology (shared ancestry), distribution, cellular communication pathways and the effects of the medicine should all be taken into account.

In order to calculate the first doses in early clinical trials and predict the therapeutic doses in later trials, non-clinical trials collect information regarding the pharmacokinetics (the action of the body on the medicine) of the candidate compound, calculations must be made based on the result from toxicology studies. In the case of biologic medicines, the calculations are often based on the body’s

response to the medicine.

When selecting an animal model, it is important to evaluate the physiology and pathophysiology of the animal species in question against that of humans. Historically healthy animals have been used to predict efficacy and safety in patients, who by their very nature of having a disease, have an altered physiology. Therefore, frequently, animal models with the disease in question are now used in non-clinical testing. Special considerations must be taken to extrapolate data to special groups such as paediatric and geriatric populations, or pregnant women.

The choice of animal species also depends on practical considerations, such as species availability and the ease with which they can be used in standardised laboratory environments and procedures. Screening tests are often applied before the animal species is selected.

Some examples of animal models include:

- rat (osteoporosis, inflammatory diseases, diabetes, obesity, cardiovascular dysfunctions, neurodegenerative diseases, cancers)
- monkey (osteoporosis, inflammatory diseases)
- pig (cardiovascular dysfunctions such as hypertension), and
- mouse (cancers, some genetic diseases)

Examples of specific animal models

In general toxicity studies (repeated-dose toxicity studies), rats and dogs are a common choice of animal model, unless they are unsuitable due to pharmacodynamic, pharmacokinetic, and/or pathophysiological differences.

For reproductive toxicology studies, rats are commonly selected for the assessment of effects on fertility, embryo-

foetal development, and pre- and post-natal toxicity. Rabbits are commonly selected as a second, non-rodent species for studies assessing the potential for embryo-foetal toxicity. If these are unsuitable, and often in the case of biotechnology products, non-human primates may be considered for these reproductive toxicology studies.

Long-term carcinogenicity studies commonly use rats, mice, or hamsters. Additional assessments of carcinogenic potential typically use transgenic mice in short-term study designs.

Other non-clinical study types address specific aspects of safety, such as addiction potential (rodents, primates), vaccines (ferrets), immunotoxicity (mice), hypersensitivity (guinea pig), and dermal, topical toxicity (pig).

For some studies, the most common models are inapplicable. In these cases, common substitutions replace rats with hamsters, gerbils, or guinea-pigs; dogs might be replaced by mini-/micro-pigs or monkeys.

In some cases, particularly with medicines derived from living organisms, it is not possible to establish a ‘relevant’ and predictive animal species, and in those cases other approaches are recommended. These alternative approaches include the use of relevant transgenic animals which express the human target, or the use of proteins that have the same structural features and gene-patterns (homologous proteins).

Attachments

- Presentation: Non-Clinical Development

  Size: 478,517 bytes, Format: .pptx

  Presentation on aspects of non-clinical development, including its aims, background activities, and the different types of non-clinical study.

A2-2.02.2-V1.1