International Journal of Toxicology
2018, Vol. 37(2) 121-124

DOI: 10.1177/1091581818760564
journals.sagepub.com/home/ijt
SAGE

Reviewing the Utility of Two Species in General Toxicology Related to Drug Development

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Abstract

As part of the safety assessment of new drugs, the use of two species (a rodent and a nonrodent) for regulatory toxicology studies is the typical approach taken for small molecules. For biologics, species selection is dictated by pharmacological relevance, and single species toxicology packages (typically using the nonhuman primate) are common. The UK National Centre for the Replacement, Refinement, and Reduction of Animals in Research and the Association of the British Pharmaceutical Industry are collaborating on a project to review the utility of two species in regulatory toxicology studies, with the aim to explore whether there are wider circumstances when data from a single species could be sufficient to enable safe progression in humans. An international working group consisting of 37 representatives from pharmaceutical and biotechnology companies, contract research organizations, academia, and regulatory bodies is coordinating a large-scale data sharing exercise to examine the potential for changes in current practice to reduce the number of species used for nonclinical safety testing at different stages of development. The challenge will be to determine whether two species toxicology adds significant value or whether in some instances data from a single species are sufficient (across a broader range of molecules than is currently the case) without compromising human safety.

Keywords

biologics, drug development, first-in-human, nonrodent, rodent, safety assessment, small molecules, toxicology

Why Do We Use Two Species in Regulatory Toxicology Studies?

It is a global regulatory requirement that potential new medicines are tested in animals for safety and tolerability prior to first-in-human (FIH) trials. This is to support the FIH dose setting and benefit/risk assessment but additionally to support longer term dosing in humans and to support special populations (eg, women of childbearing potential, children, etc). Regulatory toxicology studies are conducted to stipulated standards (eg, Good Laboratory Practice compliance) and follow recommendations within various regulatory guidances[1-3] as appropriate to the particular molecule and intended therapeutic application. Potential new medicines come from a large and diverse range of molecules, which includes new chemical entities ("small molecules"), new biological entities ("large molecules" or biologics), vaccines, and others. Small molecules are chemically derived, while large molecules are typically protein-based and derived from cells, including antibody-based products such as monoclonal antibodies (mAbs). Similar general concepts apply to any drug in development, but due to the nature of differences between investigative new drugs, there can be diverse approaches in the nonclinical safety testing strategy, which includes the number of species used for regulatory general toxicology (this project does not include reproductive toxicology or carcinogenicity testing considerations).

For small molecules, the use of two species (a rodent and a nonrodent) for toxicological assessment is mandated by regulatory guidance (eg, in ICHM3(R2), ICHS9). This strategy has evolved over many decades from multispecies testing concepts[4] (summarized by Monticello et al[5]) and a thorough approach for safety evaluation has been shown to be warranted.[6] For large molecules, two species toxicology is also mandated; however, the selection of species may be limited by

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pharmacological relevance (eg, the presence of a highly specific epitope). The nonhuman primate (NHP) is often the only species relevant for regulatory general toxicology studies, and therefore, single species toxicology programs are common.[7] Nevertheless, if a large molecule does demonstrate cross-reactivity with multiple species (including rodent), then toxicology testing using two species is required (examples in the paper by Sewell et al and Blaich et al[8,9]). Provided the toxicity profile is identical in short-term toxicology studies, it is possible to justify assessment of chronic toxicity in a single species only (typically rodent), although there seems to be no published evidence to confirm that this scenario is being adopted. There are also disease-specific guidance documents for certain drugs, which also have to be taken into account along with ICHM3 or ICHS6, as applicable. For example, the guideline for development of oncology pharmaceuticals[3] provides guidance on a reduced scope for the nonclinical toxicology program, with a view to accelerate the development of new therapies for advanced cancer. Although ICHS9 indicates toxicology testing in two species is still generally expected, it does contain examples where consideration for development in a single species might be possible for certain molecules.

The species used for small molecules are generally the rat and dog,[6,10,11] although the mouse, minipig,[12] NHP, and others can be used as alternatives when these are considered to be the more relevant species (with regard to pharmacological relevance, pharmacokinetic/metabolic profiles, and/or class-related tolerability/precedents).[6] The use of two phylogenetically unrelated animal species may increase the likelihood of detection of adverse effects in humans.[13] Reviews of nonclinical data indicate that nonrodent data identify toxicities additional to those detected in rodents for packages supporting FIH trials,[11,14,15] whereas a specific analysis of 20 anticancer compounds found that the rodent and nonrodent were equally sensitive for detection of human adverse events.[16] Comparisons of target organ toxicities from short-term ($\leq$3 months) and long-term ($\geq$3 months) dosing studies also found it equally likely that the rodent and nonrodent species detected new or increased severity toxicities.[17,18]

Purpose of the Project

The UK National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs) and the Association of the British Pharmaceutical Industry (ABPI) are collaborating on a project to review the utility of 2 species in regulatory toxicology studies and to explore circumstances when data from a single species could be sufficient to enable safe progression in humans, at different stages of development. The use of two species for regulatory toxicology studies is the normal approach for small molecules, based on regulatory guidance. For biologics, species selection is dictated by pharmacological relevance, and as outlined above, single species toxicology programs (typically using the NHP) are common. Therefore, it is pertinent to continue to review approaches used and challenge thinking, in this case asking questions including:

- Could single species approaches be used more broadly across a wider range of molecules?
  - To support the FIH clinical studies?
  - To support continued clinical development through to marketing application?
- Might it be possible to conduct some development programs with two species and move to one or vice-versa?
  - For example, two species to support the FIH studies but 1 species for support of chronic clinical dosing?
- Are the current guidelines and access/use of scientific advice (or equivalent) meetings with regulatory agencies appropriate to support flexible strategies and challenging approaches such as single species use for a wider range of molecules?

Our intention is to consider whether different approaches may be applied to the number of species used for nonclinical safety testing, for example, within specific classes of compounds, therapeutic indications, or phases of development. Additionally, new opportunities may become apparent by reviewing standard and case-by-case examples and sharing these more widely across the industry.

Compounds For Review and Process Plans

The pharmaceutical and related industries are proactive in reviewing requirements, justifying the relevance of current testing strategies, and identifying opportunities for adoption of new or different approaches which may provide more predictive data and of course apply 3Rs principles to the use of animals. Other consortia have, or are actively considering, specific questions which align with and/or complement this project, including the predictivity of nonclinical to clinical (FIH) data,[13] predevelopment attrition of pharmaceuticals,[19] the appropriate use of animals for mAbs,[8,20] and other biotherapeutics development,[9] among others. Within this busy collaborative environment, it is realized that any new data analysis should not duplicate or replicate other initiatives but identify a unique topic/question or opportunities to supplement and expand the overall picture.

A working group has been established, bringing together 37 representatives from international pharmaceutical and biotechnology companies, contract research organizations, academia, and regulatory agencies (covering Europe and the United States). The aim of the working group is to undertake a data sharing exercise and to collect information on the species used and types of toxicology studies conducted over the course of (1) late discovery/candidate selection phases (pre-FIH general toxicology packages), (2) the general toxicology studies to support Investigational New Drug (IND) phase I trials (FIH package), and (3) the general toxicology studies to support longer term dosing phase II/III trials (post-FIH package). The

types of compounds selected include small molecules and biologics that are currently in or have recently stopped development in any of the 3 categories described. Some of the data collected will be quantitative (eg, target class, therapy area, numbers and types of studies performed, types of target organ toxicities observed). Other information will be qualitative (eg, the impact of each study on decisions made, retrospective considerations around whether data from the second species [if used] added value or if use of a single species would have been justified). In order to reduce inadvertent selection bias within the data set, participating companies were asked to provide data from the most recent compounds in their portfolios, dating back no further than 2012. The main data set collection period was May to August 2017, and after collation by the UK NC3Rs, the working group initiated review of all data in late 2017. Further publications will describe the results of this initiative, provide recommendations for industry and regulators to consider, and discuss the implications for future safety studies for drug development.

In conclusion

Flexibility in current drug development practices and regulations allows the most appropriate approaches to be taken for individual drug candidate programs, and following established routines provides a high level of volunteer and patient safety. Reviews of industry data can promote best practice approaches, identifying new and/or efficient/streamlined ways of working, which may also create opportunities for replacement, refinement, or reduction in animal use within the drug development process. The challenge for this project will be to determine whether two species toxicology adds significant value or whether data from a single species could be justified (across a broader range of molecules than is currently the case) without compromising human safety. Considered together with the work of other consortia, these projects illustrate the willingness of the industry and regulators to collaborate toward a more flexible, science-based regulatory safety testing approach in the future.

Authors' Note

This article is coauthored and cofunded by the Nonclinical Biological Discovery Expert Network (NaBDEN) of the ABPI, working in partnership with the NC3Rs. The article represents the policies of the ABPI. ABPI represents the research-based pharmaceutical industry in the United Kingdom, and its NaBDEN expert group covers nonclinical issues in pharmaceutical research and drug development—developing strategy, monitoring policy and responding to consultations. In particular, it focuses on discovery, preclinical safety, animal research, and welfare.

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The NC3Rs is an independent scientific organization. It supports the UK science base by driving and funding innovation and technological developments that replace or reduce the need for animals in research and testing and lead to improvements in welfare where animals continue to be used. The Centre promotes robust and ethical scientific practice through collaborating with research funders, academia, industry, regulators, and animal welfare organisations, both in the United Kingdom and internationally.

Author Contributions

All authors made equal contributions to the drafting and reviewing of this publication. H. Prior contributed to conception and design, contributed to acquisition, analysis, and interpretation, and drafted the manuscript. P. Baldrick contributed to conception and design and critically revised the manuscript. L. De Haan contributed to design, contributed to interpretation, and critically revised the manuscript. N. Downes contributed to design, contributed to interpretation, and critically revised the manuscript. K. Jones contributed to conception and design and drafted the manuscript. E. Mortimer-Cassen contributed to design and critically revised the manuscript. I. Kimber contributed to conception and design and drafted the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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