National Centre for the Replacement Refinement & Reduction of Animals in Research

Are we fully exploiting the use of a single species for post-'first-in-human' (FIH) studies allowed within ICHS6?

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Introduction

The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) and the Association of the British Pharmaceutical Industry (ABPI) are collaborating to investigate if two species are still required for toxicology testing in the current industry landscape, and whether existing opportunities to use a single species are being fully exploited and/or could be expanded[1].

For safety assessment of biologicals, single species toxicology programmes are common (often using NHPs), but if cross-reactivity with multiple species is demonstrated, toxicology testing using two species is required. Within ICHS6 guidelines, one species (preferably rodent) may be used for longer-term studies if toxicity profiles are 'similar' in two species during short-term studies.

Here we present the incidence of one or two species use across current portfolios following ICHS6 and a detailed analysis of target organ toxicities identified at first-in-human (FIH) stage. This has determined the incidence of 'similarity' in toxicities between species tested and identified a broader potential for reducing to one species for molecules following ICHS6.

Methods

Data were collected by questionnaire from May to August 2017. Participants submitted information from their most recent molecules to have completed packages of toxicology studies (performed post-2012 to reflect current guidelines). No compound-identifying factors (names or chemical structures) were collected and all data were blinded upon receipt at the NC3Rs.

The dataset was sorted to identify molecules that used two species for short-term (2-13 week) toxicology studies to support FIH submission. The target organ toxicities in the two species were compared and noted as 'none', 'same', 'similar' or 'different' (see footnote to Table 1). No assessment of severities or relative importance of target organs for decision-making was made.

Results

Eighteen organisations submitted data for 172 compounds: 92 small molecules and 3 synthetic peptides that followed ICHM3 or ICHS9 guidelines (data not shown); and 46 monoclonal antibodies (mAbs), 15 recombinant proteins, 10 synthetic peptides and 6 antibody-drug conjugates (ADCs) that followed ICHS6 guidelines.

Molecules covered a wide range of therapy areas, including oncology (24), immunomodulation (15) and endocrinology (13). They had progressed to either pre-FIH studies (9), FIH packages (48) or post-FIH longer-term studies (20).

The molecules used one (Figure 1a) or two species (Figure 1b) during the toxicology package. Two ADCs and three mAbs reduced to a single species before the FIH package.

For molecules with FIH data in two species (13 mAbs, 11 recombinant proteins, 9 synthetic peptides and 4 ADCs), toxicities were similar ('none', 'same' and 'similar' definitions combined) in both species for 85%, 36%, 42% and 25% per molecule type respectively (Table 1). Of the 11 molecules that progressed to post-FIH studies, four mAbs, one recombinant protein and one synthetic peptide had similar toxicities at FIH, but of these, only two mAbs reduced to one species (Table 2).

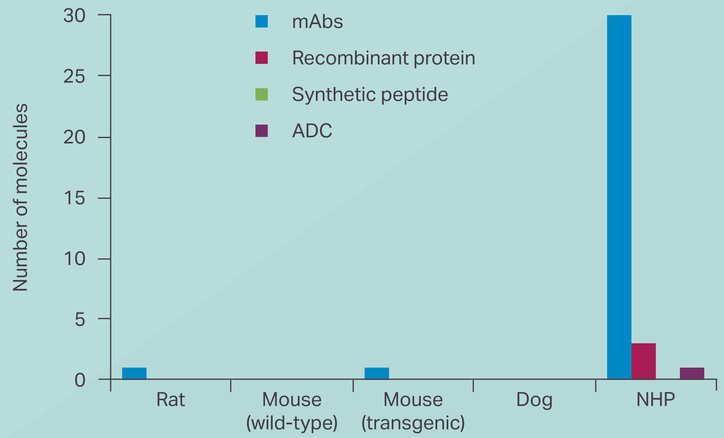

Figure 1a: Use of a single species by molecules following ICHS6 (at any phase).

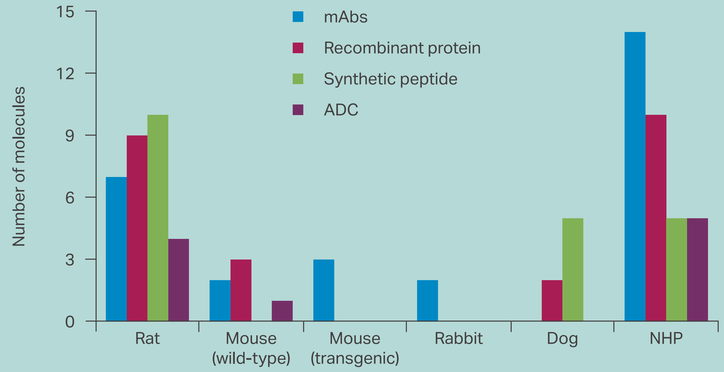

Figure 1b: Use of two species by molecules following ICHS6 (at any phase).

	None	Same	Similar	Different
mAb (13)	8	3	-	2
Recombinant protein (11)	1	1	2	7
Synthetic peptide (12)	4	-	1	7
ADC (4)	-	1	-	3

Table 1: Target organ toxicities identified in the two species for FIH studies.

Definitions of the table categories

None = absence of target organ toxicities in both species.

Same = toxicities identified in the same target organs in both species.

Similar = toxicities in both species, mostly the same (only one additional or different target organ toxicity in one of the species).

Different = no target organ toxicities in one species and at least one in the other species, or more than one target organ toxicity different in the two species.

Molecule type	Toxicities in the two species at FIH	Species used for post-FIH studies
mAb	None	Rat only
mAb	None	Mouse and NHP
mAb	None	Rat and NHP
mAb	Same	Rat only
mAb	Different	Rat and NHP
mAb	Different	Mouse and NHP
Recombinant protein	None	Mouse and NHP
Recombinant protein	Different	Mouse and NHP
Synthetic peptide	Similar	Rat and NHP
Synthetic peptide	Different	Rat and NHP
Synthetic peptide	Different	Rat and NHP

Table 2: Species used for post-FIH studies (molecules following ICHS6)

Discussion

A high proportion of biologicals do use two species within their regulatory toxicology packages, particularly the recombinant proteins, synthetic peptides and ADCs. Toxicities were similar at FIH for a large proportion of these. Opportunities therefore exist for more biologicals to reduce to one species for post-FIH studies.

Acknowledgements

The project is co-funded by the Nonclinical Biological Discovery Expert Network (NaBDEN) of the ABPI, working in partnership with the NC3Rs. We thank the members of the working group for permission to use their blinded data and for time spent analysing and discussing the data.

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References

[1] Prior H *et al.* (2018). Reviewing the Utility of Two Species in General Toxicology Related to Drug Development. *International Journal of Toxicology* 37: 121-124.