Reviewing the use of two species in toxicology studies supporting drug development

P19-13

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Introduction

The UK National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs) and the Association of the British Pharmaceutical Industry (ABPI) are collaborating to review the use of two species in regulatory toxicology studies.

The purpose is to explore circumstances in which data from a single species could be sufficient to enable safe progression in humans, for a broader range of molecule types than is current practice and at different stages of development.

An international working group was convened in 2017, consisting of representatives from 25 pharmaceutical and biotechnology companies, 4 contract research organisations, 2 consultancies, 2 academic bodies and 4 regulatory bodies (Europe and USA).

Here we present brief preliminary results from the data sharing exercise conducted to gather information on current practices, species used and the value of data from two species.

Methods

Data were collected by questionnaire from May to August 2017. Participants were requested to submit information from their most recent molecules to have completed packages of toxicology studies (performed post-2012 to reflect current guidelines) at the following stages of progression:

a) Pre-First-in-Human (FIH): molecules that have completed early non-Good Laboratory Practice (GLP) studies, but have not yet started FIH studies

b) FIH: molecules that have completed pivotal GLP studies

c) post-FIH: molecules that have completed pivotal long-term studies

No molecule-identifying factors (names or chemical structures) were collected and all data were blinded upon receipt at the NC3Rs.

Results

Eighteen organisations submitted data for 172 molecules (Figure 1): 53% from USA-, 44% from Europe- and 3% from Japan-based companies. The dataset includes five different molecule types (Figure 1) and multiple therapeutic indications (Figure 2).

114 molecules were in active development whilst 58 had stopped (Table 1). The majority of molecules (93) had completed the FIH package of toxicology studies, whilst a further 47 were in later development and had conducted post-FIH longer-term toxicology studies.

Two species were used for 97% (89) of the small molecules, 80% (12) of the recombinant proteins, 100% (13) of the synthetic peptides and 83% (5) of the antibody-drug conjugates (ADCs), but only 30% (14) of the monoclonal antibodies (mAbs), as shown in Figure 3. The different rodent and non-rodent species used are illustrated in Figures 4a and 4b.

For molecules using two species (Table 2), one small molecule (following ICHM3 guidelines), five mAbs and two ADCs (all following ICHS6 guidelines) reduced to a single species during the package. All other molecules retained use of two species: 94 followed ICHM3 or ICHS9 guidelines whilst 31 followed ICHS6 guidelines (including 11 molecules at post-FIH stage).

Discussion

This data provides a starting point to examine how many species need to be used for regulatory toxicology studies, and if the typical two species approach could be replaced more frequently with a one species approach.

For small molecules, two species use was the common approach (as expected), irrespective of therapeutic indication. For large molecules, single species use was evident in many cases (some mAbs), but not for others (recombinant proteins, synthetic peptides and ADCs). For these molecules, where two species had been used initially, there were few incidences of reducing to one species in later stages of development.

Understanding the differences or similarities in toxicities between species may highlight reasons for the low adoption of opportunities within current regulatory guidelines (e.g. single species chronic studies for biologicals) and may provide evidence to promote consideration of the use of one species to a wider range of molecule types (e.g. small molecules) or therapeutic areas (e.g. oncology).

Supporting human safety is the key focus of regulatory toxicology studies and the opportunity to use one species, or reduce from two to one species, requires careful consideration. Further analysis of and reflection on the complete dataset is ongoing.

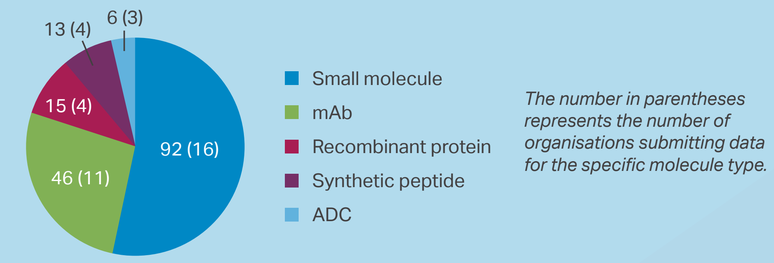

Figure 1
Total number of compounds per molecule type within the dataset.

The number in parentheses represents the number of organisations submitting data for the specific molecule type.

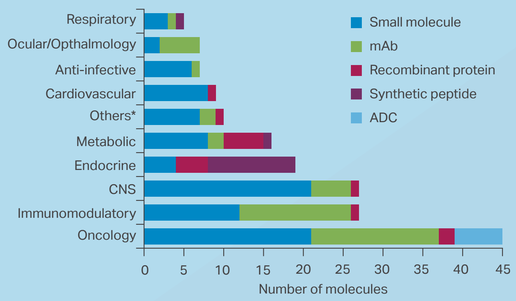

Figure 2
Therapeutic indications of the molecules within the dataset.

** includes not disclosed (3), bleeding disorders/ haematology (2), urology (3), gastrointestinal (1) and gynaecology (1).*

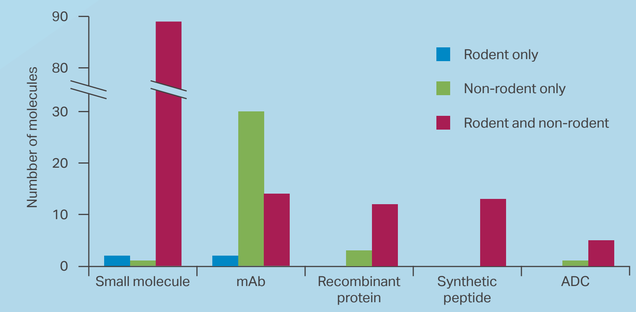

Figure 3
Number of species used for each molecule type.

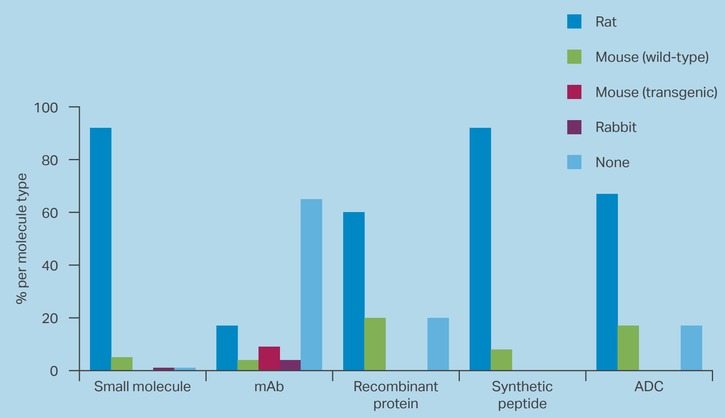

Figure 4a
Rodent species used for each molecule type.

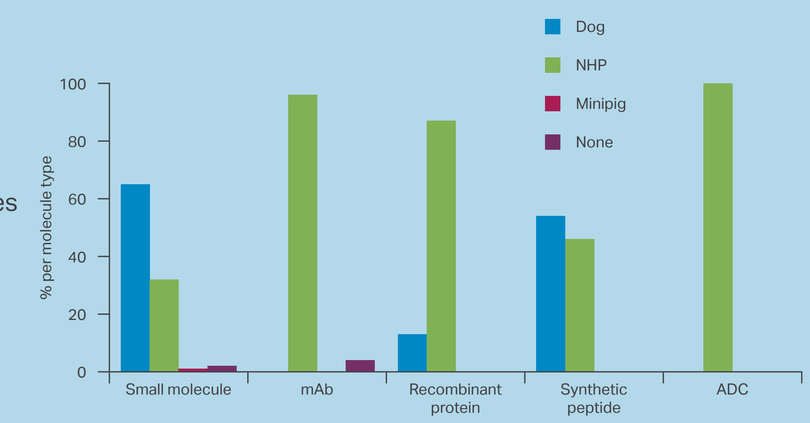

Figure 4b
Non-rodent species used for each molecule type.

Table 1: Distribution of molecules across the three phases of toxicology studies.

	Number of molecules in active development				Number of molecules stopped in development			
	Pre-FIH	FIH	Post-FIH	Total	Pre-FIH	FIH	Post-FIH	Total
Small molecule	12	26	25	63	11	18	0	29
mAb	0	19	10	29	1	11	5	17
Recombinant protein	3	4	1	8	1	5	1	7
Synthetic peptide	2	3	5	10	0	3	0	3
ADC	0	4	0	4	2	0	0	2
Total for phase	17	56	41	114	15	37	6	58

Table 2: Reduction from two to one species for different molecule types at the three stages of progression.

	Guidelines followed				Molecules at pre-FIH	Molecules at FIH	Molecules at post-FIH
	Total	ICHM3	ICHS6	ICHS9			
Small molecule	89	68		21	0 / 21	0 / 43	**1** / 25[a]
mAb	14		14		**1** / 1[b]	**4** / 7[c]	**2** / 6[d]
Recombinant protein	12		12		0 / 3	0 / 7	0 / 2
Synthetic peptide	13	3	10		0 / 2	0 / 6	0 / 5
ADC	5		2*	3	0 / 1	**3** / 4[b]	

* these molecules also followed ICHS9 guidelines. [a] progressed in dog only; [b] progressed in NHP only; [c] one progressed in rat and three in NHP only; [d] both progressed in rat only.

Acknowledgements

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