Use of recovery animals for human safety assessment across the pharmaceutical development package

P19-15

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Introduction

It is a regulatory requirement to assess recovery (whether effects observed persist or reverse once treatment ends) at some point during drug development. However, it is not stipulated how, where or when recovery animals should be included (if at all). In 2014, it was recommended that inclusion later in development should be considered, as more information on toxicity is available[1].

As part of the NC3Rs/ABPI (Association of the British Pharmaceutical Industry) initiative to review the use of two species in regulatory toxicology packages[2], an international expert group comprising 37 pharmaceutical/biotechnology companies, contract research organisations and regulatory bodies has provided data to examine current approaches to the inclusion of recovery animal groups.

Results

In the 2017 dataset, recovery data were available for 62 small molecules and 39 monoclonal antibodies (mAbs) for studies conducted to support First-in-Human (FIH) and later phase clinical trials. The dataset from the 2014 publication comprised 78 small molecules and 50 mAbs.

Comparison of FIH packages (2017 *vs.* 2014)

Overall, fewer studies included recovery to support FIH in the 2017 dataset than in the 2014 publication.

In the 2017 dataset, there were more examples of molecules only including recovery animals in some studies to support FIH packages (rather than all studies), and also more examples of molecules where recovery was not assessed in any study at all (Figure 1 and Table 1).

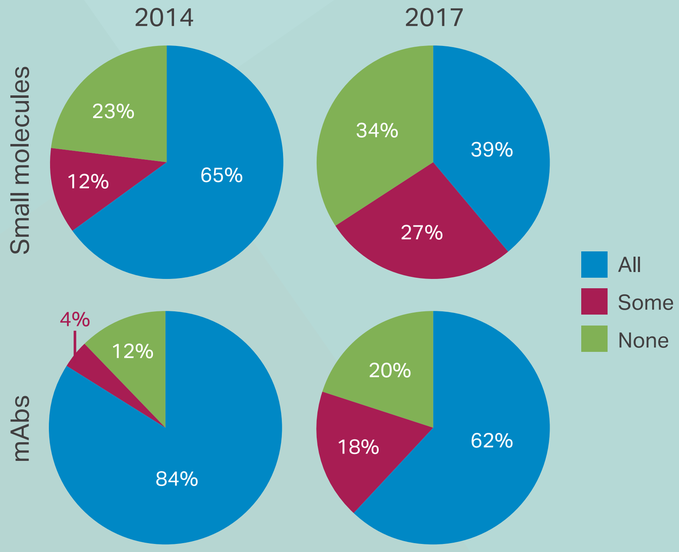

Figure 1: Percentage of molecules where recovery animals were included in all, some or no studies to support FIH packages.

	2014	2017
Small molecules	78 small molecules (163 studies)	62 small molecules (159 studies)
	111/163 (68%) studies included recovery	83/159 (52%) studies included recovery
	60/78 (77%) molecules included recovery in at least one study to support FIH, usually for both toxicology species	41/62 (66%) molecules included recovery in at least one study to support FIH, usually for both toxicology species
	18/78 (26%) molecules did not include recovery in any study to support FIH	**21/62 (34%) molecules did not include recovery in any study to support FIH**
mAbs	50 mAbs (79 studies)	39 mAbs (60 studies)
	64/79 (81%) studies included recovery	40/60 (67%) studies included recovery
	44/50 (88%) molecules included recovery in at least one study to support FIH, **usually in NHP**	31/39 (80%) molecules included recovery in at least one study to support FIH, **usually in NHP**
	6/50 (12%) molecules did not include recovery in any study to support FIH	**8/39 (20%) molecules did not include recovery in any study to support FIH**

Table 1. Comparison between the 2014 and 2017 datasets for small molecules and mAbs.

Looking at study design when recovery animals were included, the 2017 dataset for small molecules included examples of both high dose group or single sex only (Figure 2A). There appears to have been an even greater change in study design for mAbs, with recovery being assessed in fewer dose groups and cases of high dose groups only being used (Figure 2B).

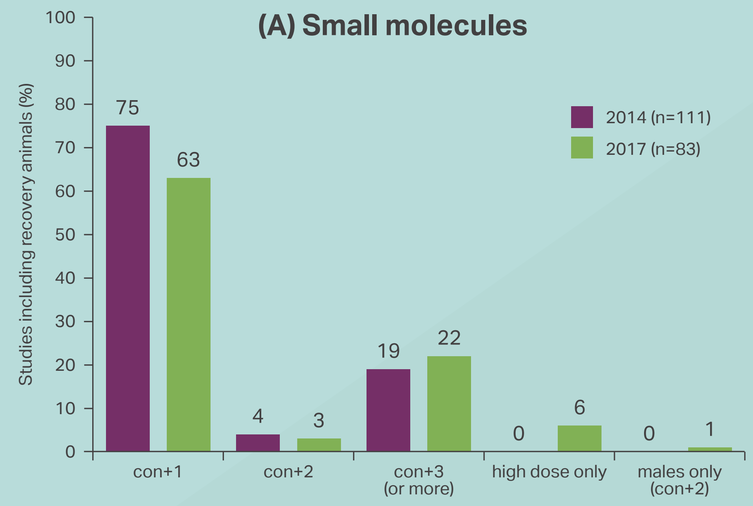

Figure 2: Comparison of study designs – inclusion of recovery animals per dose group for small molecules and mAbs. Control plus one (con+1), two (con+2), three (con+3) dose groups.

FIH and post-FIH packages (2017 dataset)

In the 2017 dataset there was information on additional studies to support post-FIH packages for 22 small molecules and 13 mAbs (Figure 3).

Small molecules – variable approaches were adopted: most included recovery groups in almost all studies, both rodent and non-rodent, for both FIH and post-FIH packages (9 compounds). However, some assessed recovery in FIH only (6 compounds) or post-FIH studies only (4 compounds). 3 compounds did not include recovery animal groups in **any** study at all, FIH or post-FIH.

mAbs – recovery animals were always included at some point: recovery groups were included in both FIH and post-FIH studies for 10 compounds, whilst for others recovery was assessed either in FIH studies only (2 compounds) or post-FIH studies only (1 compound).

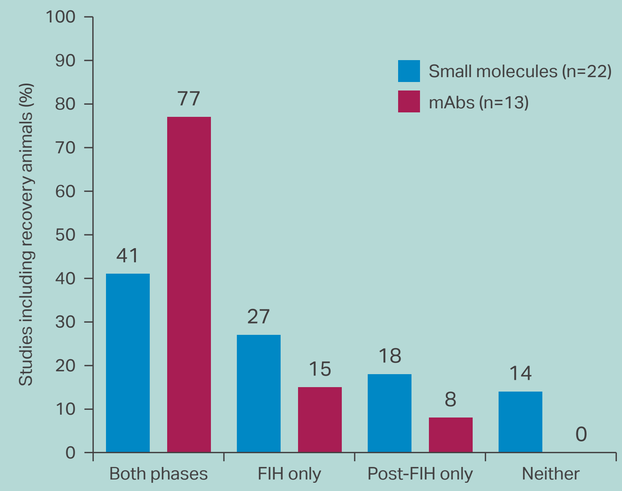

Figure 3: Percentage of molecules that included recovery animal groups in studies to support FIH, post-FIH, both or neither.

Conclusions

Compared to 2014, recovery animal groups are being included in fewer studies, and in fewer dose groups. There are more examples of recovery animals not being included in any study to support FIH.

Industry is moving towards a more case-by-case approach, however there remain opportunities to expand uptake of the previous recommendations, and reduce the use of recovery animals across the wider drug development pathway without impacting on human safety.

References

[1] Sewell *et al.* (2014). Recommendations from a global cross-company data sharing initiative on the incorporation of recovery phase animals in safety assessment studies to support first-in-human clinical trials. *Regulatory Toxicology and Pharmacology* 70: 413-429.

[2] Prior *et al.* (2018). Reviewing the utility of two species in general toxicology relating to drug development. *International Journal of Toxicology* 37(2): 121-124.