Trends toward a reduction in the use of recovery animals for First-In-Human (FIH) studies from 2013 to 2017

Fiona Sewell (✉ fiona.sewell@nc3rs.org.uk), Nichola Gellatly and Helen Prior
National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs), London, UK

Introduction

It is a regulatory requirement that recovery is assessed during pharmaceutical development, to assess whether effects observed persist or reverse once treatment ends. However, there is flexibility as to how, where, or even *if* recovery animals are included.

In 2014, a data-sharing initiative identified opportunities to reduce recovery animal use by inclusion later in development, and in fewer studies or dose groups[1].

A recent NC3Rs/ABPI (Association of the British Pharmaceutical Industry) international working group, comprising 37 pharmaceutical/biotechnology companies, contract research organisations and regulatory bodies, reviewing two species use within toxicology studies[2] has also collected data on the use of recovery animals, providing an insight into current trends.

Results

Data from 157 studies (started 2014 onwards) to support FIH clinical trials were compared with 242 studies (the pre-2014 dataset).

There was a reduction in the proportion of studies including recovery animals compared with the earlier dataset – 49% *vs.* 68% for small molecules, and 55% *vs.* 81% for monoclonal antibodies (mAbs).

When recovery groups were included, the number of small molecule studies with control and/or high dose only were similar to previous data (76% *vs.* 75%), but mAbs showed an increase in studies with control and/or high dose only (50% *vs.* 33%), away from recovery in all dose groups. The newer dataset also included examples of inclusion in high dose only (no control) for both molecule types.

	Pre-2014	2014 onwards
Small molecules	78 small molecules (163 studies)	48 small molecules (117 studies)
	111/163 (68%) studies included recovery	57/117 (49%) studies included recovery
	60/78 (77%) molecules included recovery in at least one study to support FIH, usually for both toxicology species	30/48 (62%) 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	**18/48 (38%) molecules did not include recovery in any study to support FIH**
mAbs	50 mAbs (79 studies)	26 mAbs (40 studies)
	64/79 (81%) studies included recovery	22/40 (55%) studies included recovery
	44/50 (88%) molecules included recovery in at least one study to support FIH, **usually in NHP.**	18/26 (69%) 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.	**8/26 (31%) molecules did not include recovery in any study to support FIH.**

Table 1: Comparison between the pre-2014 and later (2014 onwards) datasets for small molecules and mAbs.

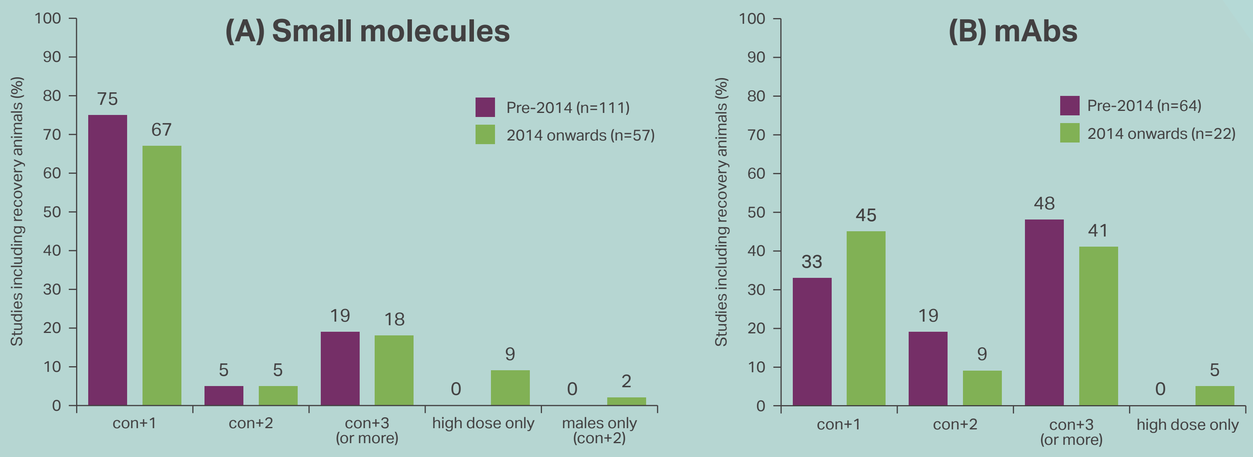

Figure 1: Comparison of study designs – inclusion of recovery animals per dose group for small molecules and mAbs. Control plus one (con+1), two (con+2), three (con+3) dose groups.

In terms of species, there was a similar reduction in the proportion of studies including recovery animals for non-human primates (NHP), rats and dogs compared with the earlier dataset.

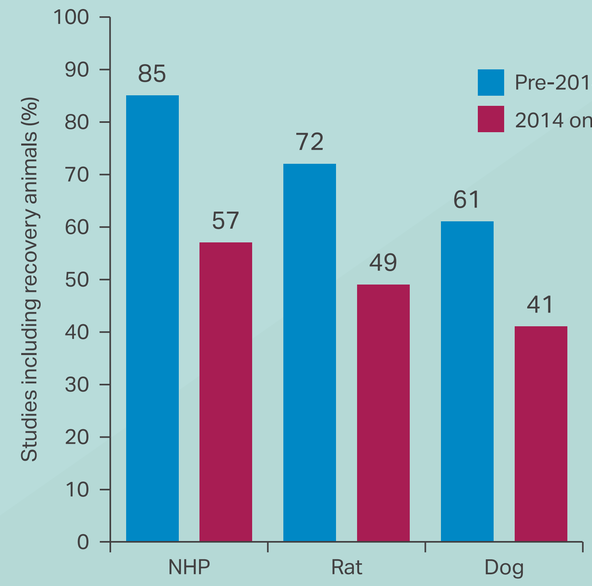

Figure 2: Proportion of studies including recovery animals by species.

Similarly, there has been a change in study design, with a reduction in the proportion of studies including recovery in more than one dose group.

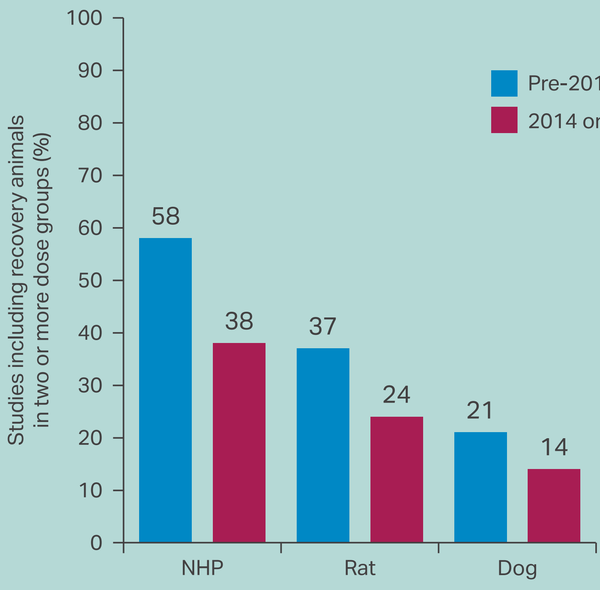

Figure 3: Proportion of studies including recovery animals in two or more dose groups.

Conclusions

There is a trend towards a reduction in recovery animal use. In the more recent dataset, when recovery was included, reduced study designs were employed with fewer dose groups and therefore fewer animals used. There are also some cases of high dose only (no control) and/or assessment in a single sex. Reductions are being seen across all species.

Although these data suggest trends toward reduced and case-specific approaches, there remain opportunities to review and further reduce recovery animal use in FIH packages without impacting human safety.

References

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