The use of recovery animals across monoclonal antibody development packages: opportunity for further optimization remains

Helen Prior and Fiona Sewell

National Centre for the Replacement Refinement & Reduction of Animals in Research (NC3Rs), London, UK

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

INTRODUCTION

- It is a regulatory requirement that recovery of adverse findings is assessed during pharmaceutical development, but there is flexibility around how and when this is performed and if recovery animals are necessary.
- For monoclonal antibodies (mAbs) following ICH S6(R1), if use of recovery animals is warranted, this need only be in one toxicity study.
- We have used data shared within a recent collaboration between the NC3Rs, the Netherlands Medicines Evaluation Board (MEB) and 14 pharmaceutical companies to review current practices for recovery animals use during mAb development.

METHODS

- Data on study designs (e.g., start date, species, recovery animal group number and sizes), for studies enabling first-in-human (FIH) dosing and longer duration studies supporting later development were collected.
- To compare with previous data [1], only mAbs with at least one study started in 2015 or later were used in this analysis; there were 52 mAbs with 83 non-human primate, 1 minipig, 4 rat, 4 mouse and 3 transgenic (TG) mouse studies in total.

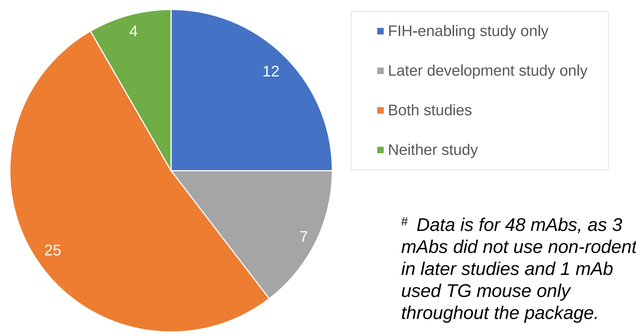
[1] Sewell F *et al.* (2014). *Reg Tox & Pharm* 70: 413-429.

CONCLUSION

- Variability in study designs suggests case-by-case approaches are used to develop many mAbs.
- Recovery is often assessed in multiple studies and multiple species.
- These data suggest assessment of recovery is more extensive than required by ICH S6(R1), and there may be an opportunity to reduce recovery animal use on many mAb programs.

RESULTS

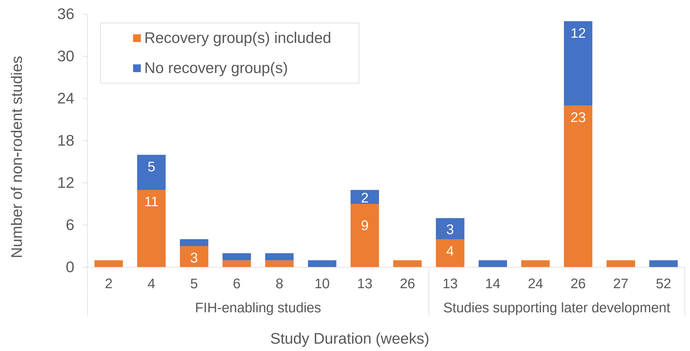
Fig 1. Inclusion of recovery groups in non-rodent studies across mAb packages#



 # Data is for 48 mAbs, as 3 mAbs did not use non-rodent in later studies and 1 mAb used TG mouse only throughout the package.

- 4 mAbs did not include recovery groups on any non-rodent study.
- Recovery groups were included on both FIH-enabling and later development studies in 52% of mAbs and on one study only (either FIH-enabling or later development study) in 40% of mAbs.

Fig 2. Recovery animal use for FIH-enabling and later development non-rodent studies



- Recovery groups were included in 27 of 38 non-rodent FIH-enabling studies (71%) and in 29 of 46 non-rodent studies supporting later development (63%).
- Recovery groups were also included in 4 of 6 rodent FIH-enabling studies (67%) and all 5 rodent studies supporting later development (100%; data not shown).

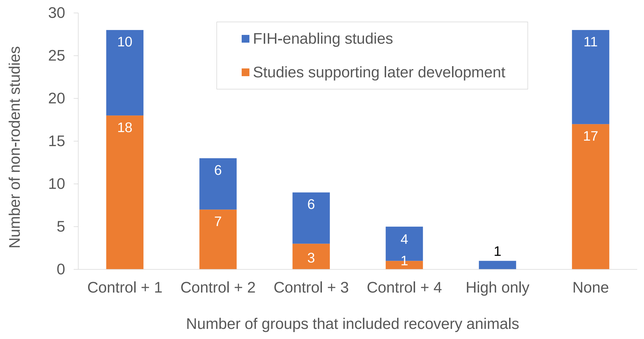
Table 1. Recovery animal use for the 8 mAbs using two species across the package

mAb ID	FIH-enabling studies	Later development studies
1	Rat (13 wk ✓) + Cynomolgus monkey (13 wk ✓)	Rat (26 wk ✓)
2	Mouse (13 wk ✓) + Cynomolgus monkey (13 wk ✓)	Cynomolgus monkey (26 wk X)
3	Mouse (2 wk X) + Cynomolgus monkey (4 wk X)	Mouse (13 wk ✓) + Cynomolgus monkey (13 wk ✓)
4	Rat (8 wk X) + Cynomolgus monkey (8 wk ✓)	Cynomolgus monkey (26 wk X)
5	Rat (8 wk ✓) + Minipig (6 wk ✓)	Rat (26 wk ✓)
6	TG mouse (5 wk X) + Cynomolgus monkey (5 wk X)	TG mouse (26 wk ✓) + Cynomolgus monkey (26 wk ✓)
7	Rat (4 wk ✓) + cynomolgus monkey (4 wk ✓)	Rat (26 wk ✓) + Cynomolgus monkey (26 wk ✓)
8	Mouse (13 wk ✓) + Cynomolgus monkey (13 wk ✓)	Mouse (26 wk ✓) + Cynomolgus monkey (26 wk ✓)

(X wk): study duration ✓ recovery groups included X no recovery groups

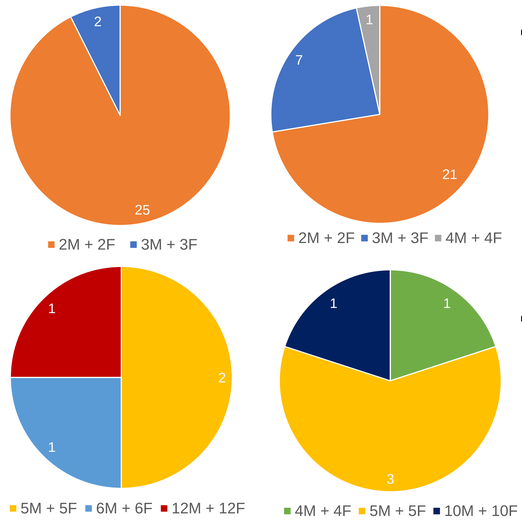
- 4 mAbs included recovery groups in all studies (both species), 3 mAbs included recovery groups in both species but for only one study duration and 1 mAb included recovery animals on only one study (non-rodent only).

Fig 3. The number of recovery animal groups when included in non-rodent studies



- Recovery animals were often restricted to control + 1 test article-dosed group, usually in high-dose.
- Many non-rodent studies included recovery on all groups (control + 3 or 4 test article-dosed groups); one study included recovery on just high-dose (no controls).
- There was also one rodent study with recovery on low-dose group only (data not shown).

Fig 4. Recovery animal group sizes



- A recovery group size of 2M+2F was used in 82% of non-rodent studies but some later development studies used higher recovery group sizes (3 or 4 per sex).
- 5M+5F was used in 56% of rodent studies. The higher group sizes (10 or 12 M+F) relate to transgenic mice studies.

Top panel: Non-rodent studies; Lower panel: rodent studies.

FIH-enabling studies on left and Later development studies on right.

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CBG MEB MEDICINES EVALUATION BOARD

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epaa The European Partnership for Alternative Approaches to Animal Testing

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For further information, please contact helen.prior@nc3rs.org.uk / fiona.sewell @nc3rs.org.uk