Global cross-company data-sharing on the use of recovery animals for human safety assessment

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Summary

- Recovery animals are included on toxicology studies to assess whether effects observed during dosing persist or reverse once treatment ends.
- It is a regulatory expectation that recovery from toxic effects will be considered at some point during the drug development process, but there is flexibility around why, when and how.
- An NC3Rs /MHRA collaboration with the pharmaceutical and biotechnology industry has collected data on the use of recovery animals in general regulatory toxicology studies to support first-in-human (FIH) trials.
- These data have been used as an evidence-base to make recommendations on the use of recovery animals in toxicology studies to inform risk assessments for administration to humans, while reducing animal use.

Data collection and results

- Data was collected by questionnaire. Questions focused on study design, the rationale behind inclusion or exclusion, and the impact this had on internal and regulatory decisions.
- Data from 137 compounds (including 53 biologicals and 78 small molecules) and 259 studies were shared by 22 companies.
- There was wide variation in where, when and why recovery animals were included. The number of recovery animals used per compound ranged from 0 to over 100.
- Recovery animals were often included in all studies (Figures 1 and 2) and in more than one dose group (Figures 3 and 4).

Biologicals

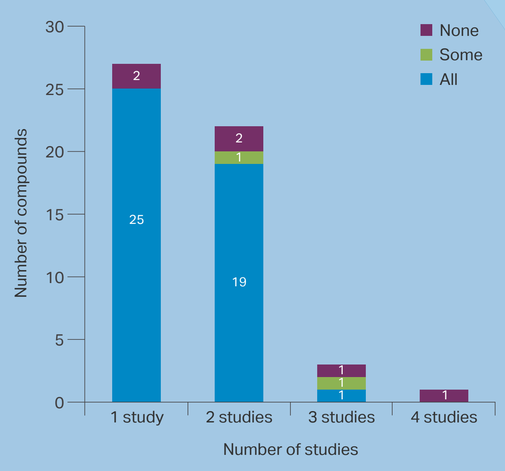

Figure 1: Biologicals - number of studies per compound and inclusion of recovery animals

Small molecules

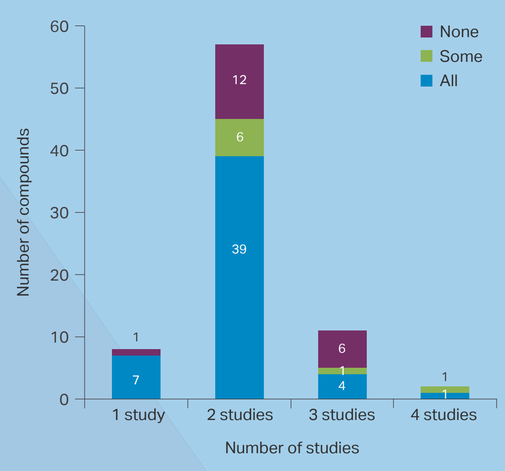

Figure 2: Small molecules - number of studies per compound and inclusion of recovery animals

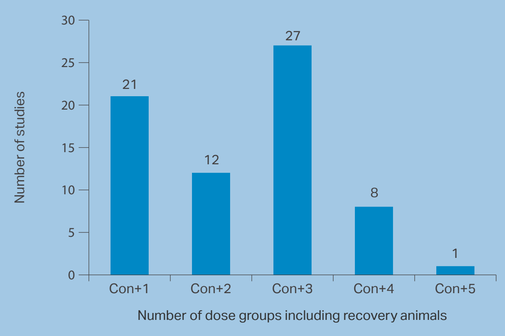

Figure 3: Biologicals - number of dose groups per study which included recovery animals

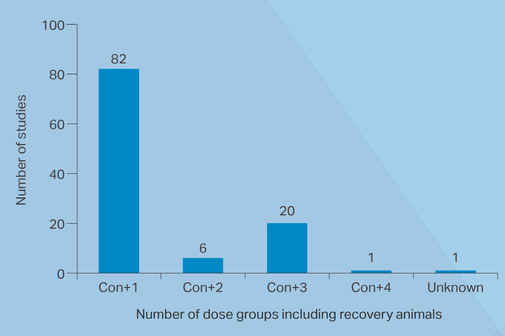

Figure 4: Small molecules - number of dose groups per study which included recovery animals

Recommendations

- Decisions to include recovery animals should be made on a case-by-case basis, by scientific assessment
- Recovery animals should only be included if there is a positive indication of need (Tables 1 and 2).
- If recovery in animal studies is required this can be assessed using a well-considered study design. Recovery animals do not necessarily need to be included in every study or every dose group (Figure 5).

Figure 5: Consideration tree for the use of recovery animals in regulatory toxicology studies

Conclusions

- There are opportunities to reduce the use of recovery animals in certain circumstances which would not impact drug development.
- Recovery animals are not necessary unless there is positive an indication of need.
- Some companies did not include recovery animals in any study and were still able to proceed to FIH trials.
- It is recognised that no single study design will be appropriate in all cases; we advocate a science-driven based approach that advances the understanding of biology and supports clinical development while minimising the use of animals.

Tables 1 and 2: Recommendations for situations where inclusion of recovery animals may or may not be warranted

Rationale for inclusion of recovery animals. Weight of evidence approach:

- Lack of prior knowledge:
  - Lack of knowledge of the reversibility of specific lesion/effect.
  - Lack of certainty of the mechanism of action (MOA).
- Literature/known class effects:
  - Indication of potentially irreversible (severe) toxicities at clinically relevant exposures .
- Previous internal non-clinical data on the compound or a related one:
  - Signal from prior *in vitro* or *in silico* study indicates that more information on reversibility is required.
  - Signal from prior *in vivo* study suggests reversibility may be a concern
  - Suggestion of severe toxicity at clinically relevant exposures
- Prior internal clinical experience with class of drug:
  - Suggests assessment of recovery is necessary (e.g. expected toxicities are not known to recover or are expected to occur at clinically relevant levels).

Situations when inclusion of recovery animals is not warranted.

Prediction of reversibility through:

- Literature or otherwise known class effects e.g:
  - Prior knowledge of the compound or class of compound and target.
  - Lesion effect known to be reversible or irreversible.
- Previous internal non-clinical data on the compound or a related one.
- Prior internal clinical experience with class of drug.
- Expert experience on the nature of the lesion and reference to literature and other sources:
  - i.e toxicity is always reversible or always irreversible.
- Known toxicities only occur at clinically irrelevant doses.

Reference

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.* Doi:10.1016/j.yrtph.2014.07.018.

3Rs impact

Potential to reduce the number of recovery animals used in thousands of regulatory toxicology studies worldwide.

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

International industry collaboration

The recommendations were developed by an international expert group which includes 30 organisations (pharmaceutical and biotechnology companies, contract research organisations regulatory bodies) from Europe and the US, led by the NC3Rs and the UK Medicines and Healthcare products Regulatory Agency (MHRA).

NC3Rs, Medicines Healthcare products Regulatory Agency (MHRA), AbbVie, Allergan, AstraZeneca, Austrian Agency for Health and Food Safety, Bayer, Biogen Idec, Celgene, Charles River Laboratories, Covance, Food and Drug Administration (FDA), Genentech, Gilead, GlaxoSmithKline, Huntingdon Life Sciences, Infinity, iMED, University of Lisbon and Infarmed, Janssen, Merck, MedImmune, Millenium, Novartis, Novo Nordisk, Paul-Ehrlich-Institut, Pfizer, Roche, University of East Finland, Vertex.