Regulatory Toxicology and Pharmacology 70 (2014) 413–429

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

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

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ARTICLE INFO

Article history:
Received 14 July 2014
Available online 29 July 2014

ABSTRACT

An international expert group which includes 30 organisations (pharmaceutical companies, contract research organisations, academic institutions and regulatory bodies) has shared data on the use of recovery animals in the assessment of pharmaceutical safety for early development. These data have

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http://dx.doi.org/10.1016/j.yrtph.2014.07.018
0273-2300/

Keywords:
Recovery
Reversibility
3Rs
Reduction
Non-clinical
Repeat-dose studies
Regulatory toxicology
Rodent
Primate
Dog

been used as an evidence-base to make recommendations on the inclusion of recovery animals in toxicology studies to achieve scientific objectives, while reducing animal use.

Recovery animals are used in pharmaceutical development to provide information on the potential for a toxic effect to translate into long-term human risk. They are included on toxicology studies to assess whether effects observed during dosing persist or reverse once treatment ends.

The group devised a questionnaire to collect information on the use of recovery animals in general regulatory toxicology studies to support first-in-human studies. Questions focused on study design, the rationale behind inclusion or exclusion and the impact this had on internal and regulatory decisions. Data on 137 compounds (including 53 biologicals and 78 small molecules) from 259 studies showed wide variation in where, when and why recovery animals were included. An analysis of individual study and programme design shows that there are opportunities to reduce the use of recovery animals without impacting drug development.

1. Introduction

1.1. Background

It is a scientific, ethical and regulatory requirement that before any potential new medicine can be administered to humans its safety must be adequately assessed in animals in order to inform safe starting doses and clinical safety monitoring for human studies. To meet this objective, repeat-dose toxicology studies in rodents and/or non-rodents are typically required by global regulatory agencies before a drug can be approved for administration to humans. These studies aim to characterise the toxicological profile of the test compound following repeated administration, including identification of potential target organs of toxicity and exposure/response relationships. This is generally achieved through the use of three dose groups (i.e. to test low, intermediate and high levels of the drug), plus a control group. Additional animals are frequently included in these studies to evaluate the reversibility or recovery of any toxicities observed during the dosing phase. Once treatment is complete, these additional animals are retained 'off-dose' for a predetermined period so that recovery can be assessed. The 'recovery phase' should be of sufficient duration for the drug to clear from circulation, and/or disengage from its receptor target, and be of adequate time to determine whether the effects observed during the treatment phase persist, or are partially or fully reversible. Demonstration of full or partial reversibility of toxicity can then be used as part of the overall assessment of the suitability of the drug for administration to humans. In rare cases, new toxicities may also be identified during the recovery phase (i.e. delayed toxicity).

Although it is a regulatory expectation that recovery from toxic effects will be considered at some point during the drug development process, this is not necessarily required prior to first-in-human (FIH) clinical trials and does not necessarily require the use of dedicated recovery animal groups. Guidance on the inclusion of recovery animals to support clinical development phases and the associated regulatory recommendations is given in the International Conference on Harmonisation (ICH) guidelines, ICH, M3(R2)*Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and the recently published accompanying *Question and Answer* document (ICH, M3(R2), ICH, M3(R2) Q&A). Guidance on the use of recovery animals for particular classes of drug include ICH S6(R1), *Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals* and ICH S9, *Nonclinical Evaluation for Anti-cancer Pharmaceuticals* (ICH, S6(R1), ICH, S9). Relevant extracts from these guidances are set out in Tables 1 and 2.

Typically, reversibility is assessed through the inclusion of additional 'recovery' animals on toxicology studies at different stages during the development programme. However, depending on the specific study objectives and the nature of the observed changes, the addition of recovery animals may not always be necessary to determine whether a toxic effect is reversible, and in many cases an evaluation of reversibility based on scientific assessment alone may be sufficient. For example, in cases where the lesions are known to be reversible, or where toxicities occur at clinically irrelevant exposure levels, demonstration of reversibility by inclusion of recovery animals may not always be necessary or justifiable. Generally, where recovery animals are considered important, they are only needed to evaluate a particular toxicity or lesion once during a development programme and on one clinically relevant dose group. The ICH M3(R2) Question and Answer document (ICH, M3(R2) Q&A) (Table 2) gives examples of occasions where inclusion of recovery animal groups may be appropriate, such as where there is severe toxicity at clinically relevant exposures. However, the guidance is intentionally flexible and does not provide specific information on when it is appropriate to include recovery animals during the drug development process.

A number of publications have examined the use of recovery animals in non-clinical toxicology studies, with a focus on the typical study designs used, including the number of dose groups that included recovery animals and the number of recovery animals per group (Baldrick, 2008; Baldrick, 2011; Brennan et al., 2010; Chapman et al., 2009; Chapman et al., 2012; Chapman et al., 2010; Clarke et al., 2008; Konigsson, 2010; Lynch et al., 2009; Pandher et al., 2012; Perry et al., 2013; Smith et al., 2005; Sparrow et al., 2011). Many of these make recommendations for appropriate study designs, stating that inclusion of recovery animals should follow a study/project specific science-driven approach to comply with the regulatory expectations whilst minimising laboratory animal use. However, the majority of the published literature focuses on studies for biological drugs conducted in non-human primates (NHPs), and/or evaluate inclusion of recovery groups for individual studies, rather than inclusion in the development package of new molecules as a whole.

Opinions and practices vary around why, when and how recovery animals should be included on toxicology studies. Given this uncertainty, recovery animals may be included by default without specific consideration of their value or scientific utility, to reduce potential perceived regulatory hurdles and/or to prevent repeating a toxicology study if unexpected toxicity is observed that might necessitate further evaluation of reversibility to support dosing in humans. The main reason for inclusion of recovery animals is to address the reversibility of an effect seen in an earlier study. However, there are also scientific reasons for the inclusion of these additional 'off-dose' animals which may not directly assess reversibility, such as to inform clinical dosing, to assess the potential for delayed toxicity, and/or to gather data on immunogenicity or PK/PD relationships. Although these reasons may not fall within the regulatory expectations with regards to the assessment of reversibility, these are examples of how 'off-dose' animals may be used