Australian Government
Department of Health
Therapeutic Goods Administration

Guidance 23: Nonclinical studies

Previously ARGPM Appendix 23:

Version 1.1, September 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Office of Medicines Authorisation	1/07/2013
V1.1	Information moved from EU guideline 3BS11a	Office of Scientific Evaluation	15/09/2014

Contents

Introduction

This guidance is to assist sponsors with submitting nonclinical studies in Module 4 of the Common Technical Document (CTD) as part of the application to register a prescription medicine on the Australian Register of Therapeutic Goods (ARTG). This guidance is **in addition to** the adopted European Union (EU) guidelines for nonclinical studies. The submitted additional information should include:

- All relevant nonclinical information, whether favourable or unfavourable to the medicine.
- Details of any incomplete or abandoned pharmacological or toxicological testing, as well as individual animal data from toxicity studies.

23.1 Additional pharmacodynamic and pharmacokinetic studies

23.1.1 Pharmacodynamics

- Establish, where possible, the mechanism of the primary pharmacological action.
- Investigate, where relevant, the pharmacology of significant metabolites.

23.1.2 Pharmacokinetics

These notes are concerned with the time course of the absorption, distribution and excretion of new medicinal products and with their metabolism in relation to their safety.

Data on the levels of substance and metabolites in blood, body fluids, organs and in the excreta can be obtained by physical, chemical or biological methods. When a labelled substance is used, the position of the label in the molecule and the specific activity of the material must be stated. Consideration should be given when selecting the position of the label to its likely metabolic fate. Attention must be given to the fact that the measured label in body fluids may not correspond to that of the unmodified substance, but may include labelled metabolites and conjugates. Attention should be given to the possibility of isotope exchange with endogenous compounds.

The animal species in these studies usually should be those used in the pharmacological and toxicological investigations. A preliminary study of kinetics and metabolism of the medicinal product in a few human subjects could provide useful information in choosing the animal species to be used in repeated dose toxicity studies.

Information should be presented on the following items:

- Absorption (fractional absorption, kinetics)
- Distribution in the principal organs and tissues and the time course in body fluids
- Blood, plasma or serum half-life
- Plasma protein binding
- Characterisation of the pattern of metabolites in excreta, and where practicable, identification of major metabolites
- Route and time course of excretion of substance and metabolites

- If biliary excretion is a major route of elimination , then the possibility of enterohepatic recycling should be investigated.

A quantitative account of the fate of the administered dose should be attempted.

To assist in the interpretation of toxicological studies, it is important to compare the exposure of the animals used in the toxicity testing with the anticipated exposure in patients under the proposed therapeutic dose regimen.

- Provide systemic exposure data for all animal species used in repeat dose, carcinogenicity and reproductive toxicity studies.
- Provide exposure data in humans at the maximum recommended dose (including, where relevant, paediatric exposure data).
- Include tables comparing these data as part of the Nonclinical Summary or Overview
- Ensure the exposure data, preferably obtained from the toxicity studies, includes:
  - the C_{max} (after a single dose and at steady state) and area under the curve (AUC) data for the parent drug and all major active metabolites, and/or
  - major pharmacologically inactive metabolites of potential toxicological significance.
- Include plasma protein binding data and assay methodology, if there are notable binding differences between nonclinical and clinical studies.

23.2 Additional toxicology studies

23.2.1 Specialised investigations

In addition to the standard investigations, special investigations for specific toxicological effects may be necessary to adequately assess safety of medicines that show specific toxicities such as:

- neurotoxicity
- cardiovascular toxicity
- hepatotoxicity
- immunotoxicity
- phototoxicity
- ocular toxicity

For therapies involving long-term administration:

- include repeat-dose toxicity studies of six months duration in rodents and nine months in nonrodents. Shorter duration toxicity studies may be appropriate in particular circumstances, such as where:
  - intermittent administration would result in exposure of short periods (e.g. medicines for migraine)
  - the intended patients have a short life expectancy (e.g. medicines for advanced cancer)
  - immunogenicity or intolerance confounds the conduct of longer term studies.

Sponsors are encouraged to investigate:

- the possible mechanism(s) underlying the changes observed in toxicity studies
- the potential reversibility of toxic changes seen in the repeat-dose studies.

23.3 Excipients

For excipients used for the first time in a medicine:

- Investigate the toxicology of the excipient as if it were a new drug substance.

For excipients already approved in a medicine registered in Australia:

- Provide additional nonclinical data for either:
  - a new route of administration
  - an increased daily dose
  - an increased strength.

For excipients that are well documented or described in a default standard pharmacopoeia, but not previously used in a medicine in Australia:

- Provide adequate data to justify the use of such excipients. This may include published material.
- Nonclinical data may also be required if the default standard does not contain sufficiently specific impurity controls to ensure that potentially toxic impurities arising from a modified or different route of synthesis are adequately controlled.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au

Guidance 23: Nonclinical studies V1.1 September 2014