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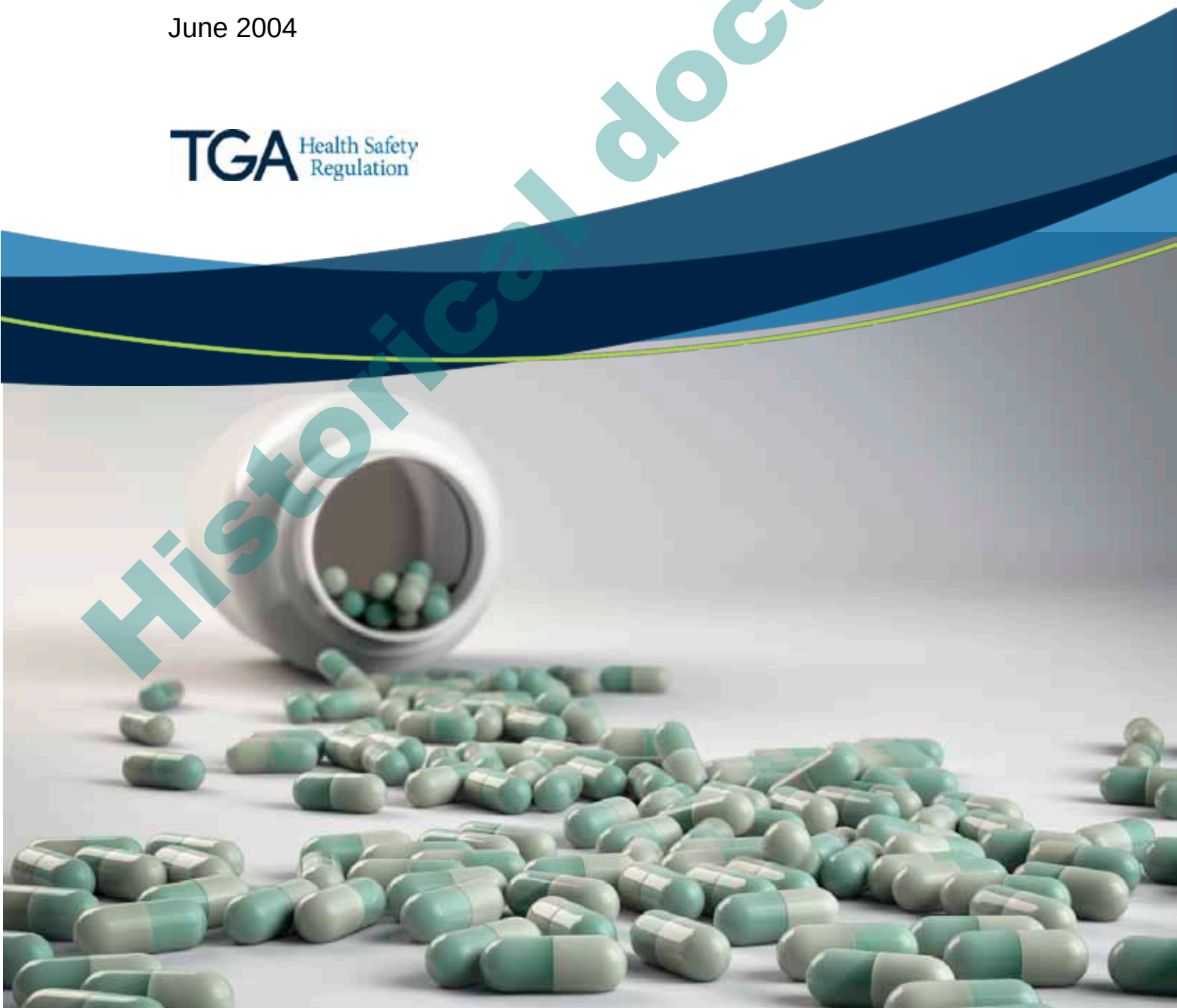
Department of Health and Ageing
Therapeutic Goods Administration

Australian regulatory guidelines for prescription medicines

Appendix 23: Supplementary non-clinical guidelines

June 2004

TGA Health Safety
Regulation



About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- 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.

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Appendix 23:

Supplementary non-clinical guidelines

These notes provide guidance as to the design, conduct and reporting of non-clinical studies and an interpretation of aspects of non-clinical EU guidelines adopted by the Therapeutic Goods Administration (TGA)¹.

1. Introduction

All information that is relevant to the non-clinical evaluation of the medicinal product concerned shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmacological or toxicological test relating to the medical product.

The toxicology and pharmacology of an excipient used for the first time in a therapeutic good should be investigated as if it were a new active substance. In the case of excipients registered in a pharmacopoeia (European, United States or British Pharmacopoeia) and other well-known excipients, which may not previously been used in Australia, adequate data to justify the use of such excipients should be provided. This may include published material. A new route of administration or an increased daily dose of known excipients may result in the need for additional non-clinical data. Non-clinical data may also be required where the monograph does not contain sufficiently specific impurity controls to ensure adequate limitation of potentially toxic impurities arising from a modified or different route of synthesis.

2. Pharmacodynamics

Where possible, sponsors are encouraged to establish the mechanism of the primary pharmacological action.

Where relevant, the pharmacology of significant metabolites should be investigated.

3. Pharmacokinetics

To assist in the interpretation of toxicological studies, it is important to compare the exposure of the animals used in the toxicity testing with that anticipated in patients given the proposed therapeutic dose regimen. Submissions should include a comparative pharmacokinetic table, for example, as part of the non-clinical summary. Such a table should include C_{max} (after a single dose and at steady state) and AUC data for the parent drug and major/active metabolite(s) where relevant. These data should preferably be obtained from the toxicity studies. Other information (for example, $t_{1/2}$, clearance, protein binding and assay methodology) will be of value where important differences have been shown between animals and man. Plasma concentration-time profiles (graphs) after a single dose, and in a dosing interval during repeat dose studies, would also be useful. Species should include human and all species used in the toxicity, carcinogenicity and reproductive studies.

¹ <http://www.tga.gov.au/industry/pm-euguidelines-nonclinical.htm>

Specificity, precision (sensitivity and reproducibility) and accuracy (for example, as regards recovery) of the assay methods should be mentioned.

4. Toxicology

Sponsors are encouraged to investigate the possible mechanism(s) underlying the changes observed in toxicity studies.

Medicines that show specific toxicological effects, such as immunotoxicity or neurotoxicity, should be investigated further. Similarly, new medicines that belong to classes that are known to produce a particular toxic effect, should be tested appropriately. The phototoxic potential of a medicine should also be considered. The details of the tests shall depend on the state of scientific knowledge at the time the application was lodged.

As a rule, the use of dosing strategies based on multiples of the proposed human dose will not be adequate.

It is desirable to investigate the potential reversibility of toxic changes seen in the repeat dose studies.

Historical document

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Reference/Publication #