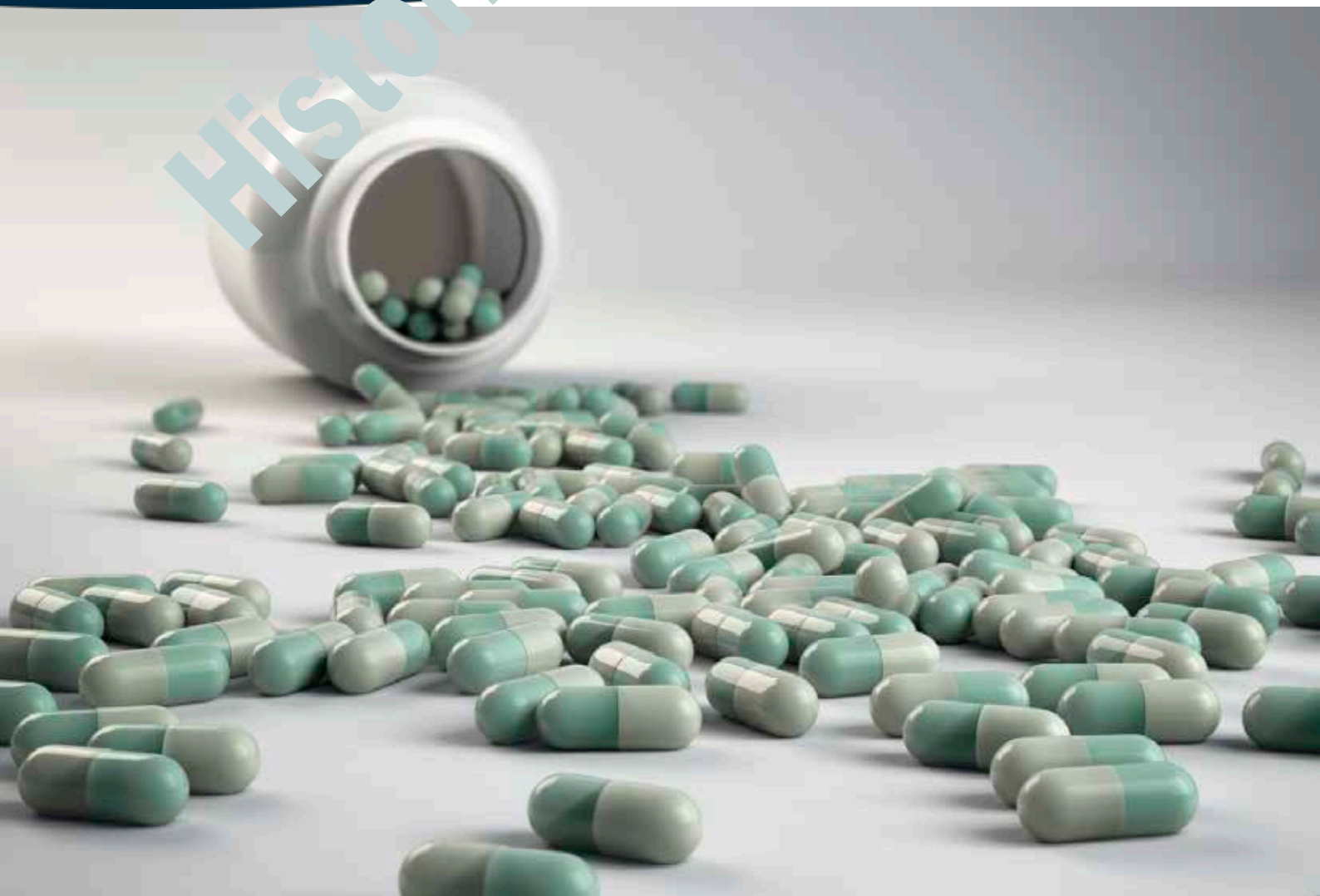
Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Access to unapproved therapeutic goods

Clinical trials in Australia

October 2004



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.

INDEX

Appendices

About this document

- This document updates *Access to Unapproved Therapeutic Goods – Clinical Trials in Australia, May 2001*.

  The changes to this document accommodate the introduction of Australia's new regulatory system for medical devices in October 2002. The changes to Australia's regulatory system for medical devices have been effected through amendment of the *Therapeutic Goods Act 1989* (the Act) and the *Therapeutic Goods Regulations 1990* (the Regulations), and through the creation of a separate set of regulations specifically for medical devices - *Therapeutic Goods (Medical Devices) Regulations 2002* (the Medical Device Regulations).

  The range of mechanisms for access to unapproved therapeutic goods remains the same following the implementation of the new medical device regulatory system, and the operation of both the CTN and CTX Schemes is unchanged.

  NOTE: The Act has been substantially restructured and is now divided into 'chapters', rather than 'parts'. The requirement for products to be entered into the ARTG has been retained. However, whereas in the past all therapeutic goods were treated the same in terms of ARTG registration or listing requirements (previously Part 3 of the Act) and manufacturing requirements (previously Part 4 of the Act), there are now separate chapters dealing with medicines (chapter 3) and medical devices (chapter 4). These chapters contain quite distinct differences in the approach to the inclusion of these products on the ARTG. Chapter 3 also captures a third set of goods, which are now known as 'other therapeutic goods' (OTGs). These are goods previously regulated as devices but which no longer satisfy the revised definition of a medical device. These products include tampons and household and hospital grade disinfectants.

  Medicines and 'other therapeutic goods' continue to be regulated as either 'registrable' or 'listable' goods, with the same TGA pre-market evaluation and manufacturer licensing requirements and procedures as previously (Sections 25, 26, 35 and 36 of the Act). The particular requirements for medical devices and the administrative processes and enforcement procedures principally aimed at ensuring those requirements are met are outlined in Chapter 4.

  At the time of introduction of the new regulatory system for devices, the legislation was framed such that, pursuant to s15A, existing mechanisms for access to unapproved medical devices provided under sections 18 and 19 of the Act continued to be operational for a period of 2 years. From October 2004, all mechanisms of access to unapproved medical devices will operate through the provisions set out in Chapter 4.

  Importantly, the new regulatory framework for medical devices excludes *in-vitro* diagnostic devices (IVDs), devices of human origin and devices containing viable cells or tissue of animal origin. Although these products fit the definition of a medical device, they have been excluded because the Australian Government is committed to developing new regulatory frameworks for them. In the interim period these products will be regulated as per the previous system, as 'other therapeutic goods'.

- This document describes the regulations for allowing patients access to unapproved medicines or medical devices by participation in a clinical trial. It is primarily directed at sponsors and investigators, but will also provide useful guidance to Human Research Ethics Committees (HRECs). HRECs are also directed to the TGA publication *Human Research Ethics Committees and the Therapeutic Goods Legislation, October 2004*.

- This document is one in a series developed by the Therapeutic Goods Administration (TGA) about the mechanisms to obtain access to unapproved therapeutic goods in Australia. The publications in this series include:

- *Access to Unapproved Therapeutic Goods - Clinical Trials in Australia* (this publication)*;*
- *Access to Unapproved Therapeutic Goods via the Special Access Scheme;*
- *Access to Unapproved Therapeutic Goods - Authorised Prescribers;* and
- *Access to Unapproved Therapeutic Goods via Personal Importation.*

The TGA has also developed a publication *Access to Unapproved Therapeutic Goods in Australia*, which is a consolidation of all the documents in the series. This should be consulted if you are unsure which is the appropriate mechanism to use.

Abbreviations and Acronyms

ADEC	Australian Drug Evaluation Committee
ADRAC	Adverse Drug Reactions Advisory Committee
AGRD	Australian Guidelines for the Registration of Drugs
AHEC	Australian Health Ethics Committee
ARTG	Australian Register of Therapeutic Goods
CIOMS	Council for International Organisations of Medical Sciences
C(PI) Regulations	Customs (Prohibited Imports) Regulations 1956
CTN	Clinical Trial Notification (Scheme)
CTX	Clinical Trial Exemption (Scheme)
DSEB	Drug Safety and Evaluation Branch, TGA
GTRAP	Gene and Related Therapies Research Advisory Panel
GTTAC	Gene Technology Technical Advisory Committee
HREC	Human Research Ethics Committee
IBC	Institutional Biosafety Committee
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
NHMRC	National Health and Medical Research Council
ODBT	Office of Devices, Blood and Tissues, TGA
OGTR	Office of the Gene Technology Regulator
OTGs	'other therapeutic goods'
the Act	*Therapeutic Goods Act 1989*
the medical devices Regulations	Therapeutic Goods (Medical Devices) Regulations 2002
the National Statement	National Statement on Ethical Conduct in Research Involving Humans, NHMRC 2007
the Regulations	Therapeutic Goods Regulations 1990
SAS	Special Access Scheme
TGA	Therapeutic Goods Administration
TGO	Therapeutic Goods Order
wd	working days

A glossary is located at **Appendix 1**.

Acknowledgement

The contribution of Medicines Australia (formerly the Australian Pharmaceutical Manufacturers Association) to the development of this guideline is greatly appreciated.

INTRODUCTION

The Legal Basis for Supply of Unapproved Therapeutic Goods

The *Therapeutic Goods Act, 1989* (the Act) and associated Regulations establishes a uniform, national system of regulatory controls to ensure the quality, safety, efficacy and timely availability of therapeutic goods for human use. Responsibility for the regulatory controls lies with the Therapeutic Goods Administration (TGA) as the national regulatory authority for therapeutic goods.

Overall control of the supply of therapeutic goods is exerted through three main processes:

- the pre-market evaluation and approval of products intended for supply in Australia;
- the licensing of pharmaceutical manufacturers and certification of device manufacturer quality systems; and
- post market surveillance.

Under the Act, therapeutic goods for human use that are imported, manufactured in Australia, supplied by a corporation, supplied interstate or to the Commonwealth, or exported must be included in the Australian Register of Therapeutic Goods (ARTG) unless specifically exempted by the Act.

Some therapeutic goods are exempted under the Act from the requirement for inclusion in the ARTG before they can be supplied. These exemptions are set out in for medicines and 'other therapeutic goods' (OTGs) in Chapter 3 Section 18 and Section 19 and for medical devices in Chapter 4 Part 4-7. The regulations relevant to these sections are:

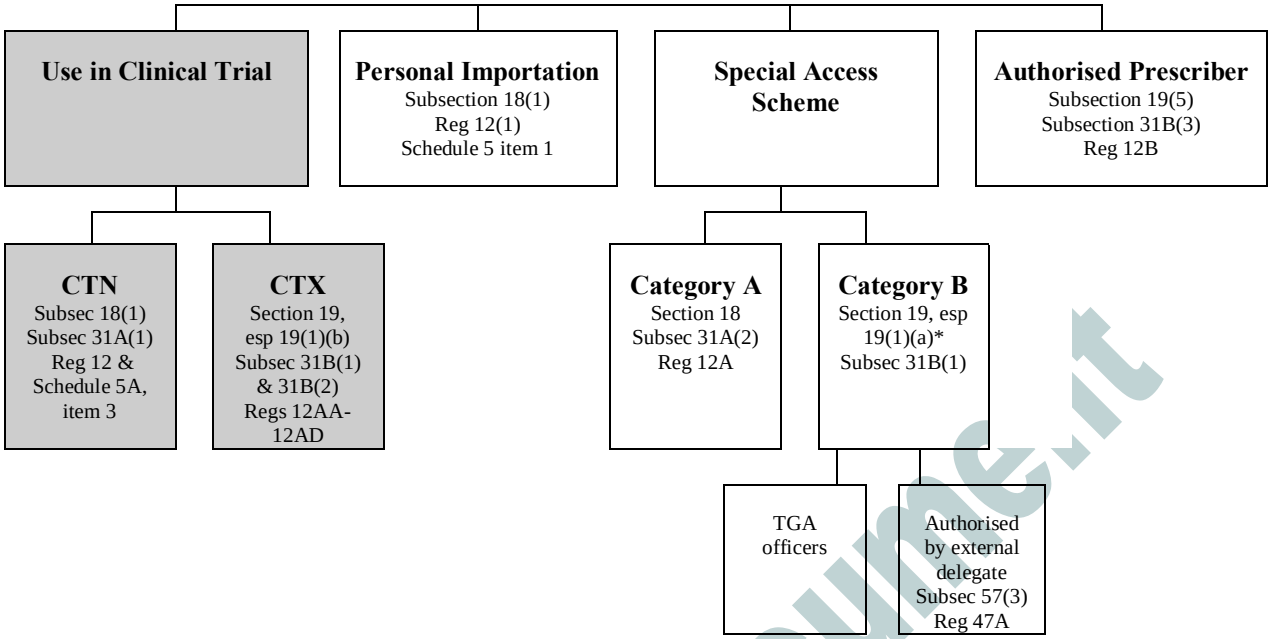
- Schedule 5 (Regulation 12(1)), Schedule 5A (Regulation 12(1A)) and Regulation 12A of the Regulations for medicines and OTGs; and
- Regulations 7.1-7.7 and Schedule 4 (Regulation 7.1) of the medical devices Regulations for medical devices.

The legislation provides the following mechanisms that allow individuals to gain limited access to therapeutic goods not on the ARTG:

- clinical trials (CTN and CTX schemes);
- the Special Access Scheme (categories A and B);
- authorised prescribers; and
- importation for personal use.

The figures below provide a graphic representation of these mechanisms and the sections of the Act and Regulations relevant to their operation. The provisions specifically relating to clinical trials have been shaded.

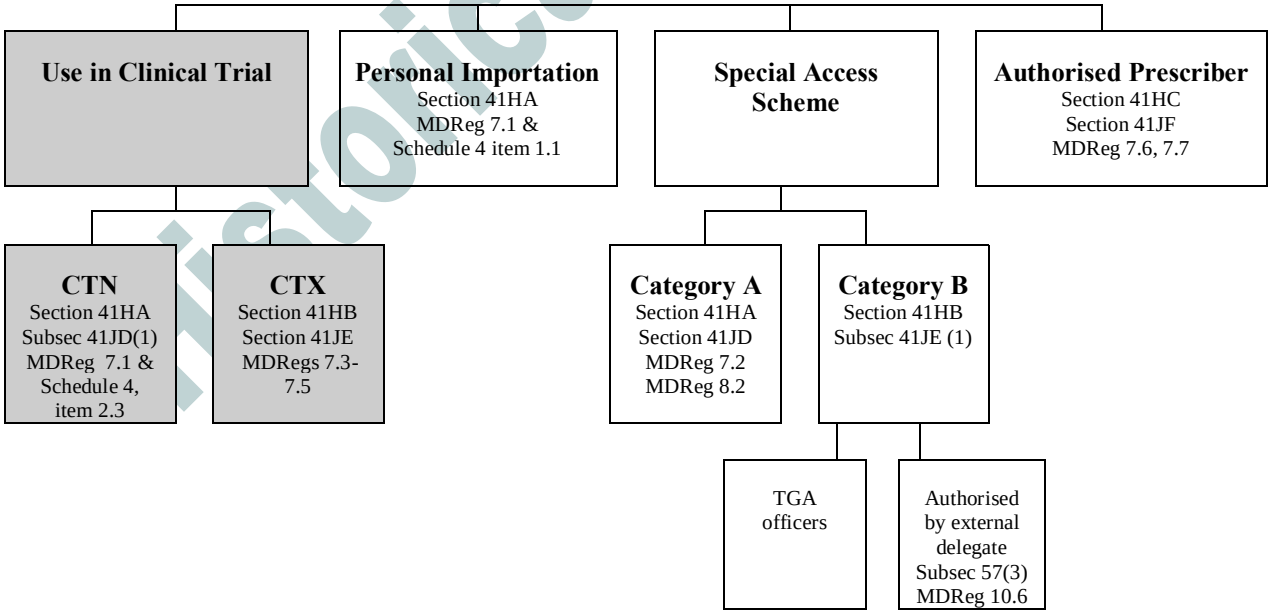
Figure 1 Access to unapproved medicines and OTGs



* Section 19 (1)(a) allows supply for Category A and Category B patients but, in practice, category A cases are dealt with under s18 and reg12A.

Reg = Therapeutic Goods Regulations 1990

Figure 2 Access to unapproved medical devices



MDReg = Therapeutic Goods (Medical Devices) Regulations 2002

Promotion of Unapproved Therapeutic Goods

The promotion of unapproved therapeutic goods is an offence under subsection 22(6) of Chapter 3 (medicines) and Section 41MM of Chapter 4 (medical devices) of the *Therapeutic Goods Act 1989* and carries a financial penalty. A person must not intentionally or recklessly make a claim, by any means, that the person or another person can arrange the supply of unapproved therapeutic goods.

Clinical trials - an Overview

A clinical trial is an experiment conducted in humans in order to assess the effects, efficacy and/or safety of a medicine, medical device, or procedure/intervention. Clinical trials of medicines and medical devices are undertaken to answer questions about their efficacy and safety. It is therefore necessary that the trial be conducted using appropriate experimental designs to obtain valid data without exposing people to unnecessary risks. The primary responsibility for monitoring a clinical trial rests with the sponsor, the institution in which the trial is being conducted and its HREC, and the investigator. Clinical trials should not be used by medical practitioners primarily as a means for obtaining an unapproved product for a particular patient. Information on other mechanisms for access to unapproved therapeutic goods is contained the TGA publication *Access to Unapproved Therapeutic Goods in Australia* and the separate TGA publications relating to each mechanism of supply. Practitioners should consult these documents for guidance if they are unsure which is the appropriate mechanism to pursue.

Procedures were established in the early 1970s to control and monitor the provision of therapeutic goods in Australia. Included was a requirement for prior approval by the Australian regulatory agency, now known as the Therapeutic Goods Administration (TGA), to conduct clinical trials in humans of new therapeutic goods or new uses of existing therapeutic goods. Over the last three decades the regulatory overview of clinical trials has evolved considerably. Today there are two routes for conducting a clinical trial of new therapeutic goods or new uses of existing therapeutic goods - the Clinical Trial Notification Scheme (CTN Scheme) and the Clinical Trial Exemption Scheme (CTX Scheme).

There is no requirement that applications to the TGA to market medicines and medical devices must contain data from clinical trials conducted in Australia. However, the Australian CTX and CTN Schemes provide considerable benefits by providing the momentum to research and develop new medicines locally and creating an environment of scientific research, and by providing early access for patients to new therapeutic developments.

It should be noted that an application or notification to conduct a clinical trial involving an unapproved therapeutic good is independent of an application for registration. A notification or application to conduct a clinical trial will be accepted whilst an application for registration of the same product is under review. Similarly, an application for registration will be accepted while a clinical trial for the same product is under review or under way in Australia.

Classification of Clinical Trials

Clinical Trials of Medicines

Clinical trials of medicines are generally classified according to the phase of the medicine's development. While individual phases may not be clearly defined, the following definitions are generally accepted and are useful for considering the context in which clinical trials are undertaken.

- Phase I studies involve the first administration of the medicine to humans, usually to small numbers of healthy volunteers. However for certain medicine classes, such as cytotoxic medicines, Phase I studies may be conducted in patients suffering from the condition the medicine is intended to treat in order to avoid unnecessary exposure of healthy individuals. The purpose of Phase I studies is to determine the safety of the medicine, its pharmacological activity, pharmacokinetics and how well it is tolerated. These studies also identify preferred routes of administration and help determine the appropriate doses for later studies. Phase I studies are usually undertaken in centres appropriately equipped for the specialised monitoring and the high degree of surveillance needed.

  Some clinical trials are conducted solely for the purpose of assessing the bioavailability of a drug or demonstrating bioequivalence of two drug products. A generic drug is one which has the same qualitative and quantitative composition, in terms of active ingredients, and the same pharmaceutical form as a marketed product and has been shown to be bioequivalent with a marketed product. Bioequivalence is said to have been demonstrated if the rate and extent of absorption of the drug into the body from the new preparation is similar to the approved product to such an extent that there will be no clinically significant difference in terms of efficacy and safety. Healthy volunteers are usually recruited for this type of study. Patients may be needed in some bioequivalence studies if the risk to healthy volunteers is too great, such as for highly toxic drugs. The efficacy and safety of the generic drug can be inferred from the characteristics of the approved product and no further clinical trials are required to support registration of the product.

- Phase II studies are the first trials of the medicine in patients suffering from the condition for which the medicine is intended. The principal aim of these studies is to determine efficacy and safety. These studies are undertaken in a small number of closely supervised patients and conducted by researchers regarded as specialists in the particular disease or condition and its treatment. Several doses of the medicine are often used to establish the therapeutic range and the maximum tolerated dose.

- Phase III studies involve greater numbers of patients and are undertaken for the purpose of determining whether the medicine confers clinical benefit in the disease/s for which effectiveness was demonstrated in Phase II studies and that the incidence and nature of adverse effects are acceptable. Phase III studies are undertaken if the Phase II studies indicate the medicine has potential benefit that outweighs the hazards.

- Phase IV studies are those studies undertaken after the medicine has been approved for marketing for the treatment of a particular disease and may include studies that seek to

compare the medicine to a wider range of therapies. This may include comparison with medicines already recognised as having a place in the treatment of the disease, or combinations of the new medicine with existing medicines (combination therapy).

Phase IV studies are also undertaken to further investigate the use of the medicine in the normal clinical setting of the disease, which may differ quite markedly from the conditions under which a pre-marketing clinical trial was conducted. This includes post marketing surveillance studies.

After a product has been placed on the market, clinical trials exploring new indications or new methods of administration are considered to be trials for new medicinal products (ie phase I, II or III trials).

Medical Device Trials

While medical device trials are not formally classified by phase, there are similarities between the stages of medical device development and medicine development. The concept of a new device is often subject to extensive preclinical testing through bench testing, biomaterials testing, immunogenicity and carcinogenicity testing and, in appropriate instances, animal testing. The invasive nature of many medical devices precludes testing in healthy volunteers, necessitating the use of animal model testing. Initial clinical testing of devices usually involves a pilot study in small groups of patients. Any use of an unapproved medical device in humans, even in pilot studies, requires an exemption from the requirement for inclusion on the ARTG, ie, supply must be through one of the mechanisms for access outlined above.

If the feasibility of the concept is proven, larger studies with well-designed protocols and a sound statistical basis are undertaken. Studies may be undertaken to confirm the performance and safety of changes in design or material of a device or to assess the device's performance against new clinical indications. The clinical safety and performance of many devices depends largely on the experience and training of the clinician using the device. These are important points for consideration in assessing a clinical trial application.

Regulation of Medicine and Medical Device Clinical Trials in Australia - An Introduction to the CTN and CTX Schemes

Clinical trials of medicines and medical devices conducted in Australia are subject to Commonwealth Government regulation administered by the Therapeutic Goods Administration (TGA).

There are two schemes under which clinical trials involving therapeutic goods may be conducted, the Clinical Trial Exemption (CTX) Scheme and the Clinical Trial Notification (CTN) Scheme. Either notification under the CTN Scheme or application under the CTX Scheme is required for all clinical investigational use of a product, where that use involves:

- any product not entered on the Australian Register of Therapeutic Goods, including any new formulation of an existing product or any new route of administration, or in the case of an existing medical device, new technology, new material or a new treatment modality; or

- use of a product beyond the conditions of its marketing approval, including new indications extending the use of a medicine to a new population group and the extension of doses or duration of treatments outside the approved range.

Clinical trials in which registered or listed medicines or medical devices are used within the conditions of their marketing approval are not subject to CTN or CTX requirements but still need to be approved by a Human Research Ethics Committee (HREC) before the trial may commence.

The CTN Scheme

Under the CTN scheme, all material relating to the proposed trial, including the trial protocol is submitted directly to the HREC by the researcher at the request of the sponsor. The TGA does not review any data relating to the clinical trial. The HREC is responsible for assessing the scientific validity of the trial design, the safety and efficacy of the medicine or device and the ethical acceptability of the trial process, and for approval of the trial protocol. In some institutions a scientific review or drug subcommittee may review the proposal before consideration by the HREC. The institution or organisation at which the trial will be conducted, referred to as the 'Approving Authority', gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC.

The TGA 'Notification of Intent to Conduct a Clinical Trial' form (the CTN Form) is submitted by the investigator on behalf of the sponsor to the HREC and to the Approving Authority. Once the sponsor, the principal investigator, the Chairman of the HREC and the person responsible from the Approving Authority have signed the CTN Form, it is submitted by the sponsor of the trial to the TGA along with the appropriate notification fee. The Therapeutic Goods Regulations require that the notification be in a form approved by the Secretary of the Department of Health and Aged Care. Sponsors must use the current CTN form (located at **Appendix 2**). Use of old (out-of-date) CTN forms will invalidate the notification.

Note: The HREC may determine that it does not wish to review the proposed trial under the CTN Scheme and recommend its review under the CTX Scheme. If an HREC feels that it requires additional expertise to review a CTN, it may seek advice from external authorities or it may seek to collaborate with another HREC that has the required expertise.

The CTX Scheme

Under the CTX Scheme, a sponsor submits an application to conduct clinical trials to the TGA for evaluation and comment. In the case of clinical trials of medicines, the TGA reviews the information about the product provided by the sponsor, including the overseas status of the medicine, proposed Usage Guidelines, a pharmaceutical data sheet, a summary of the preclinical data and clinical data. For medical device trials the TGA examines the design specifications and preclinical data.

The TGA Delegate decides whether or not to object to the proposed Usage Guidelines for the product. If an objection is raised, trials may not proceed until the objection has been addressed to the Delegate's satisfaction. Even if no objection is raised, the Delegate usually provides comments on the accuracy or interpretation of the summary information supplied by

the sponsor. The sponsor must forward these comments to the HREC(s) at sites at which the sponsor intends to conduct trials under the CTX.

The sponsor may conduct any number of clinical trials under the CTX application without further assessment by the TGA, provided use of the product in the trials falls within the original approved Usage Guidelines. However, HREC approval of each protocol and approval from the institution/organisation for the conduct of each trial are still required. The HREC in each host institution/organisation is responsible for approving the proposed trial protocol after reviewing the summary information received from the sponsor and any additional comments from the TGA Delegate. The institution or organisation concerned (the 'Approving Authority') gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC.

A sponsor cannot commence a CTX trial until:

- written advice has been received from the TGA regarding the application; and
- approval for the conduct of the trial has been obtained from an ethics committee and the institution at which the trial will be conducted.

There are two forms, each reflecting these separate processes (Parts), that must be submitted to TGA by the sponsor. Part 1 constitutes the formal CTX application. It must be completed by the sponsor of the trial and submitted to TGA with data for evaluation. Part 2 is used to notify the commencement of each new trial conducted under the CTX as well as new sites in ongoing CTX trials. The Part 2 form must be submitted within 28 days of the commencement of supply of goods under the CTX. There is no fee for notification of trials under the CTX scheme.

Applications can be lodged simultaneously with the TGA and the institution(s) at which studies are proposed to be conducted. However, if the application is lodged simultaneously with the TGA and HREC(s), the sponsor is required to convey any TGA comments or revisions on the application and/or objections to all the HREC(s). It is important to note that the application submitted to the TGA does not include the clinical trial protocol(s). The primary responsibility of the TGA is to review the safety of the use of the product and the HREC is responsible for considering the scientific and ethical issues of the proposed clinical trial protocols.

CTN or CTX?

The choice of which scheme to follow (CTN or CTX) lies firstly with the sponsor and then with the ethics committee that reviews the protocol and provides advice to the "Approving Authority" which decides whether the trial is allowed to proceed. The determining factor for an HREC is whether the Committee has access to appropriate scientific and technical expertise in order to assess the safety of the product.

As a general rule, phase III, IV and bioavailability/bioequivalence studies of medicines are most suited to the CTN scheme. However, the CTN Scheme can also be an option for earlier phase (I & II) studies if there is adequate preclinical review available, especially of safety. For medical device trials, the CTX scheme may be more appropriate where the experimental device introduces new technology, new material or a new treatment concept which has not

been evaluated previously in clinical trials in any country. However, so long as adequate guidance is available to give an HREC confidence that it has the competence to make a decision based on scientific advice, there is no reason why the CTN route could not be considered for any study.

An HREC may determine that it does not wish to review the proposed trial under the CTN Scheme and recommend its review under the CTX Scheme.

The Role of HRECs in the Regulation of Clinical Trials

The information contained in this section should be read in conjunction with the TGA publication *Human Research Ethics Committees and the Therapeutic Goods Legislation* and the *National Statement on Ethical Conduct in Research Involving Humans*, NHMRC 2007 (the National Statement).

The responsibilities of HRECs in relation to both the CTN and the CTX Schemes for clinical trials are established in the Regulations to the Therapeutic Goods Act.

For medicines and other therapeutic goods (OTGs) these are contained in the *Therapeutic Goods Regulations 1991* (the Regulations) and for medical devices in the *Therapeutic Goods (Medical Devices) Regulations 2002* (the medical devices Regulations).

Medicines and OTGs - CTN

Item 3(c) of Schedule 5A of the Regulations states that the approval for the conduct of a trial must be given by the sponsor or the body or organisation conducting the trial for the sponsor, having due regard to the advice of the ethics committee responsible for monitoring the trial. Item 3(d) requires that the terms of approval for the trial by the 'Approving Authority' be no less restrictive than the terms advised by the HREC.

Item 3(c) establishes the role of the ethics committees to monitor trials for which it has approved a protocol. Consequent to this, item 3(f) states the sponsor must not have received advice from the ethics committee that is inconsistent with the continuation of the trial.

Note: One of the conditions under which therapeutic goods supplied in a CTN trial are exempt from registration is that the sponsor of the trial or the institution/organisation conducting the trial for the sponsor, must not receive, or have received, advice from the HREC that is inconsistent with the continuance of the trial. The receipt of such advice from an HREC by the sponsor or the Approving Authority means that the unapproved goods are no longer exempt from inclusion on the ARTG. Therefore, they cannot be lawfully supplied as unapproved goods and the trial at the site at which that HREC has jurisdiction must be terminated by either the sponsor or institution. In the case of multicentre trials, it is possible that an HREC at one trial site may request termination of the trial because of site-specific issues, such as inadequate supervision by an investigator. Such a situation would not require termination of the trial at other sites. See also, "Preventing or stopping a trial"

Item 3(g) states that the conditions set out in Regulation 12AD apply to CTN trials as well as to CTX trials. Regulation 12AD sets out that the standards expected for all clinical trials are Good Clinical Practice as adopted by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals (ICH) and the Committee for Proprietary Medicines (CPMP), the protocol as approved by the HREC and the National Statement as adopted by the NHMRC.

In signing a CTN form and approving a clinical trial protocol, the HREC accepts responsibility for monitoring the progress and conduct of the trial. This is a significant ongoing role for the HREC and one that the Therapeutic Goods Regulations impose solely on the HREC.

Medicines and OTGs - CTX

Regulations 12AA, 12AB, 12AC and 12AD set out the same conditions as Item 3 Schedule 5A of the Regulations. Thus the role of the HREC for CTX trials is similar to that for CTN trials.

Regulation 12AA sets out that the TGA may seek from an HREC the names of the members of the HREC and the principal investigator or the person in charge of the trial at a site if not the principal investigator. They may also request details of any conditions that may have been specified by the HREC.

Regulation 12AB sets out the requirements for notifying each trial conducted under the CTX Scheme to the TGA. It also states that each trial must be conducted in accordance with Good Clinical Practice as adopted by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals (ICH) and the Committee for Proprietary Medicines (CPMP). This regulation also states that those conducting clinical trials under the CTX must give a written undertaking to comply with any inquiry or audit of the clinical trial which is undertaken by TGA. The sponsor and investigator in signing the CTX notification form give this written undertaking.

Regulation 12AC sets out the actions that may be taken by the TGA during an audit of a clinical trial.

Regulation 12AD sets out the conditions that are applied to clinical trials. These conditions are that the trial must be conducted in accordance with Good Clinical Practice, the protocol approved by the HREC and the NHMRC's National Statement. The clinical trial must cease if the HREC notify the principal investigator that the conduct of the trial is not in accord with the protocol or any conditions they may have specified in their approval of the protocol.

HRECs also need to be aware of relevant State and Territory laws pertaining to the supply of therapeutic goods.

Medical Devices - CTN

The Medical Devices Regulations mirror those for medicines and thus the role of the HREC in medical device trials is similar to that for trials of medicines.

Item 2.3 of Schedule 4 of the medical devices Regulations is similar to Item 3 of Schedule 5A of the Regulations. The same requirements are established for HRECs and approving authorities in approving a clinical trial for a medical device as for a clinical trial for a medicine.

Item 2.3(c) establishes the role of the ethics committees to monitor trials for which it has approved a protocol. Consequent to this, Item 2.3(f) states the sponsor must not have received advice from the ethics committee that is inconsistent with the continuation of the trial.

Item 2.3(g) states that the conditions set out in Regulation 7.5 apply to CTN trials as well as to CTX trials. Regulation 7.5 sets out that the standard expected for all clinical trials of medical devices is the National Statement.

Medical Devices - CTX

The regulations regarding clinical trials conducted under the CTX scheme are set out in Regulations 7.3, 7.4 and 7.5 of the medical devices Regulations.

Regulation 7.3 sets out the requirements for notifying each trial conducted under the CTX Scheme to the TGA. It also states that each trial must be conducted in accordance with the National Statement on Ethical Conduct in Research Involving Humans. This regulation also states that those conducting clinical trials under the CTX must give a written undertaking to comply with any inquiry or audit of the clinical trial which is undertaken by TGA. The sponsor and investigator give this written undertaking in signing the CTX notification form.

Regulation 7.4 sets out the actions that may be taken by the TGA during an audit of a clinical trial.

Regulation 7.5 sets out the conditions that are applied to clinical trials. These conditions are that the trial must be conducted in accordance with the protocol approved by the HREC and the National Statement as adopted by the NHMRC. The clinical trial must cease if the HREC notify the principal investigator that the conduct of the trial is not in accord with the protocol or any conditions they may have specified in their approval of the protocol.

HRECs also need to be aware of relevant State and Territory laws pertaining to the supply of therapeutic goods.

Other considerations

The National Statement outlines requirements and obligations of HRECs when they consider and reach decisions regarding clinical trials as follows:

- general guidance in Section 2;
- guidance specifically in relation to clinical trials and trial protocols in Section 12;
- obligations relevant to monitoring of clinical trials for both HRECs and their institutions in guidelines 2.33 - 2.38 and 12.9;
- obligations of the HREC in relation to suspension or discontinuation of research in guidelines 2.44, 2.45 and 12.10.

Trials Involving Gene Therapy and Related Therapies

The information in this section should be read in conjunction with the NHMRC *Guidelines for Ethical Review of Research Proposals for Human Somatic Cell Gene Therapy and Related Therapies* and the Gene and Related Therapies Research Advisory Panel's (GTRAP) *Recommendations for the Writing of Gene Therapy Proposals*.

Every research protocol involving gene therapy or related therapies requires approval from both an HREC and GTRAP, an expert committee established by the National Health and Medical Research Council (NHMRC) as follows:

- All such proposals must be submitted to an HREC for initial ethical review and scientific review. When it has completed its assessment, the HREC forwards the proposal to GTRAP, having identified any aspects of the proposal requiring specific comment;
- GTRAP assesses the proposal and, before giving its recommendations to the HREC, may consult with other bodies concerned with monitoring the safety of innovative genetic manipulation techniques (Office of the Gene Technology Regulator (OGTR)) or the standards for product manufacture (TGA);
- The proposal must be submitted to the TGA under the CTX Scheme unless GTRAP agrees that the research can be conducted under the CTN Scheme;
- Proposals that fall under the jurisdiction of the OGTR must also be submitted to an Institutional Biosafety Committee (IBC) for initial assessment. When it has completed its assessment, the IBC forwards its proposal to the OGTR, having identified any aspects of the proposal requiring specific comment;
- The OGTR assesses the proposal and, before giving its recommendations to the IBC, may consult with GTRAP or other bodies concerned with monitoring the safety of innovative genetic manipulation techniques; and
- The HREC ensures that the proposal has been approved by all relevant bodies and decides whether or not the research may proceed.

For a gene or related therapy trial to proceed under the CTN Scheme, GTRAP would need assurance of acceptable quality safety and efficacy. The GTRAP's *Recommendations for the Writing of Gene Therapy Proposals* advises that such assurance may be provided if:

- The product has already been evaluated and approved by the TGA (ie for a different indication). In this instance it would be important to demonstrate that the manufacture and procedures for assuring quality and safety were unchanged. The investigator would need to demonstrate comparability of the proposed doses and route of administration with those used in the approved trial.
- The product has been approved by another country's regulatory agency (with the same standards of drug evaluation as the TGA) for a clinical trial involving the same indication and route of administration. As above, issues relating to manufacture, dosage and route of administration would need to be addressed. Minor changes in manufacture may be acceptable.
- The product has been approved by another competent authority for a clinical trial for a different indication – the investigator would need to justify why the overseas approval should apply to the current application (for example, with respect to intended dose and route of administration) and also show that manufacture and certification methods were either unchanged or changed to an extent that did not significantly alter the quality, safety or efficacy of the product.

The national regulatory agencies currently regarded as having the same standards of drug evaluation as the TGA are those of the United States of America, Canada, Sweden, the United Kingdom and The Netherlands. Further information about GTRAP is available from the NHMRC Internet website (http://www.nhmrc.gov.au/research/gtrap.htm).

Good Clinical Practice

There are well established codes of Good Clinical Practice which clearly define the standards for designing, conducting, recording and reporting of medicine and medical device trials. Adherence to these codes by sponsors, investigators and HRECs is necessary for the protection of participants' rights and their well being and safety. Compliance with these codes is also important for ensuring the data generated from clinical trials are scientifically and ethically valid.

Many of these codes have been consolidated under the International Conference on Harmonisation (ICH) process. Australia has adopted the CPMP/ICH *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95). This Code of Good Clinical Practice states:

> "Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected…and that the clinical trial data are credible…The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects."

This code outlines the role of the investigator, sponsor and HREC in relation to the preparation for and conduct of a clinical trial. It is important to note that the ICH guideline makes numerous references to the need for compliance with local regulatory requirements. The TGA has reproduced the ICH GCP guidelines annotated to indicate specific local regulatory requirements. This document is available on the TGA website at the following:

http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm

Thus, before granting approval to conduct a clinical trial, all parties must be satisfied that the conduct of the proposed trial is in accordance with:

- the NHMRC *National Statement on Ethical Conduct in Research Involving Humans* (2007);
- the current World Medical Association *Declaration of Helsinki*;
- the CPMP/ICH *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95) or the ISO 14155 Clinical Investigation of Medical Devices, whichever is applicable;
- the requirements of the Therapeutic Goods Administration as outlined in this document; and
- any requirements of relevant Commonwealth and/or State/Territory laws.

All parties involved in the planning, design, conduct and monitoring of clinical trials should familiarise themselves with the contents of these documents.

Preventing or Stopping a Trial

A clinical trial of an unapproved medicine or medical device cannot be legally conducted in Australia without an initial and continuing endorsement of the trial by the responsible HREC, the "Approving Authority" and the sponsor of the clinical trial. For example, an HREC may withdraw endorsement of a clinical trial if it becomes aware of a serious risk to patient safety. In such cases, the HREC will advise the sponsor of the trial and/or the senior decision making body within institution/organisation at which the trial is being conducted of such withdrawal. The HREC should also inform the TGA of the withdrawal of its approval.

One of the conditions under which therapeutic goods supplied in a CTN trial are exempt from registration is that the sponsor of the trial or the institution/organisation conducting the trial for the sponsor must not receive or have received advice from the HREC that is inconsistent with the continuance of the trial. The receipt of such advice from an HREC by the sponsor or the Approving Authority means that the goods are no longer exempt from inclusion on the ARTG. Therefore, they can no longer be lawfully supplied and the trial must be terminated by the sponsor or institution. It follows that withdrawal of the endorsement of any of these parties will ultimately result in the termination of a clinical trial.

Similarly for CTX trials the trial must stop if the HREC advises the investigator and/or the institution that the use of the drug or device is inconsistent with the protocol or any condition which may have been specified for the trial. This includes any inconsistency with Good Clinical Practice or the National Statement.

Circumstances that may lead to withdrawal of support for a trial are most likely to arise as a result of the monitoring process. These include:

- evidence of significant deviation from the trial protocol and that, as a result, the welfare and rights of participants are not or will not be protected;
- evidence that allowing the trial to continue carries an unacceptable risk of death, serious illness or serious injury to trial participants;
- evidence from progressive review of a comparative study shows that one treatment proves to be so much better or worse that to continue the trial would disadvantage one group of participants; and
- evidence that the conduct of the trial is in breach of Commonwealth, State and/or Territory Laws.

In addition, the TGA (as delegate of the Secretary of the Department of Health and Ageing) may stop a trial where that action is in the public's interest. For example, this may be in circumstances where the trial is not being pursued in accordance with the *Therapeutic Goods Act 1989* and Regulations, or where it comes to notice that allowing the trial to proceed/continue carries an unacceptable risk of death, serious illness or serious injury. Under the Act, the TGA has the authority to inquire into and/or audit clinical trials where necessary on safety grounds and to investigate non-compliance with Good Clinical Practice standards, the National Statement, the protocol or any other legislative requirements.

In signing the CTN Form or CTX Part 2 form, the sponsor, principal investigator, HREC and Approving Authority agree to make all relevant records available to the TGA on request and to cooperate with any TGA investigation.

While the audit powers of clinical trials conducted via CTX are set out in Regulation 12AC they are applied to CTN via the powers in Part 5A of the Therapeutic Goods Act. Thus the same conditions for conduct of a trial apply to CTN and CTX and the TGA may audit clinical trials conducted under either Scheme.

If any party involved in a clinical trial has concerns over the conduct of that trial, they should contact the Experimental Drugs Section (telephone (02) 6232 8106) for medicines and the Office of Devices, Blood and Tissues (telephone (02) 6232 8679) for medical devices to discuss options available to them.

Indemnity and Compensation

When considering a clinical trial proposal, HRECs need to be satisfied trial participants will be adequately compensated for the costs of any injury suffered as a result of participation in the clinical trial. HRECs evaluate compensation arrangements to verify that they satisfactorily protect the interests of participants and the institution/organisation. The terms of the available compensation should be explained to prospective trial participants.

The HREC should also be familiar with the NHMRC *Report on Compensation, Insurance and Indemnity Arrangements for Institutional Ethics Committees.*

Because of concerns about legal liability arising from the approval of or the conduct of clinical trials, it is essential that the relationships between sponsors, investigators and institutions/organisations be clearly defined by legal and financial agreements. Such agreements should cover responsibilities for compensation and treatment of participants in the case of injury or death and for any indemnity to cover the liability of each of the parties involved. HRECs may request and review any legal agreements that exist between the sponsor and researcher.

Medicines Australia (formerly the Australian Pharmaceutical Manufacturers Association) has published *Guidelines for Compensation for Injury Resulting From Participation in a Company-sponsored Clinical Trial (February 1997)* and a *Form of Indemnity for Clinical Trials (February 1997).* These Guidelines are available from the Medicines Australia website:

http://www.medicinesaustralia.com.au

THE LEGISLATIVE BASIS FOR CLINICAL TRIALS

Act and Regulations Governing the Supply of Unapproved Therapeutic Goods in Clinical Trials

Medicines intended for use in clinical trials are exempt from registration or listing by either Section 18 or Section 19 of the *Therapeutic Goods Act 1989* (the Act), or by the operation of Regulation 12 and Schedules 5 and 5A to the *Therapeutic Goods Regulations 1990*. Medical devices intended for use in clinical trials are exempt from inclusion in the ARTG by either Section 41HA or Section 41HB of the Act and by Part 7 of the *Therapeutic Goods (Medical Devices) Regulations 2002* and Schedule 4 to the medical devices Regulations.

The therapeutic goods legislation is restricted in its coverage by constitutional limitations of Commonwealth powers. It does not cover clinical trials sponsored by unincorporated bodies or individuals using therapeutic goods wholly manufactured in the State or Territory in which they are used. Such trials would, however, be subject to the usual requirements of individual ethics committees and any relevant State or Territory legislation.

The full copy of the legislation is available at the following website:

http://www.tga.gov.au/industry/legislation.htm

Summary of Specific Provisions in the *Therapeutic Goods Act 1989* and *Therapeutic Goods Regulations 1990* for Medicines and 'Other Therapeutic Goods'

The CTN and CTX Schemes for clinical trials of medicines and OTGs have distinct legislative bases. The CTX Scheme is specifically provided for in Section 19 of the *Therapeutic Goods Act 1989*, whereas the CTN Scheme relies on the more general powers of Section 18:

- **CTN Scheme Legal Arrangements**

The Act:

18 Exempt goods

(1) The regulations may, subject to such conditions (if any) as are specified in the regulations, exempt:
  (a) all therapeutic goods, except those included in a class of goods prescribed for the purposes of this paragraph; or
  (b) specified therapeutic goods; or
  (c) a specified class of therapeutic goods;
from the operation of this Part (except section 31A and sections 31C to 31F).

(2) An exemption in terms of paragraph (1)(a) has effect only in relation to such classes of persons as are prescribed for the purposes of this subsection.

(3) Where the regulations revoke an exemption, the revocation takes effect on the day, not being earlier than 28 days after the day on which the regulations are made, specified in the regulations.

31A Secretary may require information etc. about goods exempt under section 18

Exempt goods for use for experimental purposes in humans

(1) If therapeutic goods are exempt under section 18(1) from the operation of this Part (except this section and sections 31C to 31F) to allow for their use for experimental purposes in humans, the Secretary may give the sponsor a written notice requiring the sponsor to give to the Secretary specified information or documents relating to one or more of the following:
   (a) the supply of the goods;
   (b) the handling of the goods;
   (c) the monitoring of the supply of the goods;
   (d) the results of the supply of the goods;
   (e) any other matter prescribed by the regulations for the purpose of this paragraph in relation to medicines of that kind.

(2) [Relates to Category A SAS]

Compliance period

(3) A notice under subsection (1) must specify a reasonable period within which the person to whom the notice is given must comply with it. The period must be at least 14 days starting on the day on which the notice is given.

The Regulations:

12 Exempt goods

(1A) For the purposes of subsection 18 (1) of the Act, the therapeutic goods or classes of therapeutic goods specified in an item in column 2 of Schedule 5A are exempt from the operation of Part 3 of the Act subject to compliance with the relevant conditions specified in column 3 of that Schedule.

Schedule 5A (excerpt)

Column 1	Column 2	Column 3
Item	Therapeutic Goods	Conditions
3	Therapeutic goods used solely for experimental purposes in humans	(a) before starting to use the goods, the sponsor must notify the Secretary: (i) in a form approved by the Secretary; and (ii) in accordance with the requirements (if any) determined by the Secretary for the form of notification; that the sponsor intends to sponsor a clinical trial using specified goods; and

(b) the notification must be accompanied by the relevant notification fee referred to in item 14 or 14A of Schedule 9; and

(c) the approval of the goods for this purpose must be given by the sponsor (if the sponsor is conducting the trial), or by the body or organisation conducting the trial for the sponsor, having regard to the advice of the ethics committee that has, or will assume, responsibility for monitoring the conduct of the trial; and

(d) the terms of the approval by the sponsor, body or organisation referred to in paragraph (c) must be no less restrictive than the terms advised by the ethics committee; and

(e) the Secretary must not, at any time:
(i) have become aware that to conduct or continue the trial would be contrary to the public interest; and
(ii) have directed that the trial not be conducted, or be stopped; and

(f) the sponsor (if the sponsor is conducting the trial), or the body or organisation conducting the trial for the sponsor, must not receive, or have received, advice from the ethics committee that is inconsistent with the continuation of the trial.

(g) the conditions set out in regulation 12AD must be complied with, as if that regulation applied to a person using therapeutic goods under this item.

· **CTX Scheme Legal Arrangements**

The Act:

19 Exemptions for special and experimental uses

(1) The Secretary may, by notice in writing, grant an approval to a person for the importation into, or the exportation from, Australia or the supply in Australia of specified therapeutic goods that are not registered goods, listed goods or exempt goods:
(a) [Relates to SAS]
(b) for use solely for experimental purposes in humans;

and such an approval may be given subject to such conditions as are specified in the notice of approval.

(1A) An approval for the purpose mentioned in paragraph (1)(b) is subject to conditions (if any) specified in the regulations. Those conditions (if any) are in addition to any conditions imposed on the approval under subsection (1).

(2) An application for an approval must be made to the Secretary and must:
(a) [Relates to SAS]
(b) in the case of an application for use of the kind referred to in paragraph (1)(b):
(i) be made in writing; and
(ii) be accompanied by such information relating to the goods the subject of the application as is required by the Secretary; and
(iii) be accompanied by the prescribed evaluation fee.

(3) Without limiting the conditions to which an approval under subsection (1) may be made subject, those conditions may include a condition relating to the charges that may be made for the therapeutic goods to which the approval relates.

(4) Where an application for an approval is made, the Secretary must, after having considered the application and, in the case of an application for the use of therapeutic goods for experimental purposes in humans, after having evaluated the information submitted with the application, notify the applicant of the decision on the application within 28 days of making the decision and, in the case of a decision not to grant the approval, of the reasons for the decision.

(4A) The use by a person for experimental purposes in humans of specified therapeutic goods that are the subject of an approval granted to someone else under paragraph (1)(b) is subject to the conditions (if any) specified in the regulations relating to one or more of the following:
(a) the preconditions on the use of the goods for those purposes;
(b) the principles to be followed in the use of the goods for those purposes;
(c) the monitoring of the use, and the results of the use, of the goods for those purposes;
(d) the circumstances in which the person must cease the use of the goods for those purposes.

[(5) – (8) Relates to Authorised Prescriber]

(9) In this section, "medical practitioner" means a person who is registered, in a State or internal Territory, as a medical practitioner.

31B Secretary may require information relating to approvals and authorities under section 19

Approval under subsection 19(1)

(1) The Secretary may give to a person who is granted an approval under subsection 19(1) in relation to specified therapeutic goods a written notice requiring the

person to give to the Secretary specified information or documents relating to one or more of the following:

(a) the supply of the goods;
(b) the handling of the goods;
(c) the monitoring of the supply of the goods;
(e) the results of the supply of the goods;
(f) any other matter prescribed by the regulations for the purpose of this paragraph in relation to medicines of that kind.

Approval under subsection 19(1) - use by another person

(2) The Secretary may give notice to a person using specified therapeutic goods that are the subject of an approval granted to someone else under paragraph 19(1)(b) a written notice requiring the person to give the Secretary specified information or documents relating to either or both of the following:

(a) the use of the goods;
(b) any other matter prescribed by the regulations for the purposes of this paragraph in relation to goods of that kind.

(3) [Relates to Authorised Prescriber]

Compliance period

(4) A notice under subsection (1), (2) …..must specify a reasonable period within which the person to whom the notice is given must comply with it. The period must be at least 14 days starting on the day on which the notice is given.

The Regulations:

12AA Applications for special and experimental uses

Without limiting the information that may be required by the Secretary under subsection 19(2) of the Act, that information may include, in relation to therapeutic goods that subject of an application under subsection 19(1) of the Act for the use described in paragraph 19(1)(b) of the Act:

(a) the names of the members of the ethics committee that has given approval for each proposed clinical trial of the goods and that will have responsibility for monitoring that conduct of each trial; and
(b) the name of, and the contact details for, the principal investigator for each trial; and
(c) the name of the person who will be in charge of the trial (or each trial site , if the trial is to be conducted at more that 1 site), unless that person is the principal investigator; and
(d) information about whether or not any conditions specified by the committee have been met.

12AB Goods imported, etc, for experimental uses

(1) For subsection 19(1A) of the Act, this regulation specifies conditions attaching to an approval for the importation or supply of therapeutic goods for use solely for experimental purposes in humans.

(2) Before any clinical trials proposed to be undertaken in relation to the goods are started, the National Manager, Therapeutic Goods Administration, must receive from the person to whom the approval is granted, and the principal investigator for each trial site:

(a) a written assurance that clinical trials will be conducted in accordance with the Guidelines for Good Clinical Practice (the **Practice Guidelines)**, as in force from time to time, published jointly by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and the Committee for Medicinal Products; and

(b) a written undertaking;

(i) to comply with requests by an authorised person, whether made before or after the start of a trial, to give information about the conduct of the trial; and

(i) allow an authorised person to do the things mentioned in regulation 12AC.

12 AC

(1) An authorised person may, in relation to a clinical trial mentioned in regulation 12AB:

(a) enter the site of the trial; and

(b) search the site and any thing on the site; and

(c) inspect, examine, take measurements of, or conduct tests on (including by the taking of samples), any thing on the site that relates to the trial; and

(d) take photographs, make video recordings or make sketches of the site or any thing on the site; and

(e) inspect any book, record or document on the site that relates to the trial; and

(f) request the principal investigator to:

(i) answer any questions put by the authorised person; and

(ii) produce any book, record or document requested by the authorised person.

(2) An authorised person is not entitled to do a thing mentioned in subregulation (1) if:

(a) the principal investigator or any other person present at the site concerned and in apparent control, requests the authorised person to produce his or hers identity card for inspection; and

(b) the authorised person fails to comply with the request.

(3) The principal investigator, or any other person present at the site and in apparent control, is entitled to observe a search conducted under paragraph (1)(b), but must not impede the search.

(4) Subregulation (3) does not prevent 2 or more areas of the site being searched at the same time.

12AD

For subsection 19(4A) of the Act, the following conditions are specified:

(a) the use of therapeutic goods in a clinical trial must be in accordance with the Practice Guidelines;
(b) the use must be comply with a procedural protocol determined by the ethics committee that gave approval for the clinical trial of the goods and that has the function of monitoring the conduct of the trail at each trial site;
(c) the use must be in accordance with the ethical standards set out in the National Statement on Ethical Conduct in Research Involving Humans, as in force from time to time, published by the National Health and Medical Research Council;
(d) the use must cease if the ethics committee mentioned in paragraph (b) informs the principal investigator that the use is inconsistent with:
  (i) the protocol mentioned in paragraph (b);or
  (ii) any condition subject to which approval for the use was given.

Summary of Specific Provisions in the *Therapeutic Goods Act 1989* and *Therapeutic Goods (Medical Devices) Regulations 2002* for Medical Devices

The CTN and CTX Schemes for clinical trials of medical devices have distinct legislative bases. The CTX Scheme is specifically provided for in Section 41HB of the *Therapeutic Goods Act 1989*, whereas the CTN Scheme relies on the more general powers of Section 41HA:

· **CTN Scheme Legal Arrangements**

The Act:

Part 4-7 – Exempting medical devices from inclusion in the Register

41H What this Part is about

There are 3 kinds of exemptions from the prohibitions in Division 3 of Part 4-11 on dealing in medical devices that are not included in the Register:

a) medical devices exempted under the regulations;
b) approval for medical devices to be used for special treatment of individuals or for experimental purposes;
c) authorisation of particular medical practitioners to supply specified medical devices.

41HA Devices exempted from inclusion in the Register

(1) The regulations may exempt from the operation of Division 3 of Part 4-11:
   (a) all medical devices, except those medical devices of the kinds prescribed for the purposes of this paragraph; or
   (b) specified kinds of medical devices.

   Note: Division 3 of Part 4-11 contains offences relating to dealing in medical devices that are not included in the Register.

(2) An exemption may be subject to conditions that are prescribed in the regulations.

   Note: Breach of the conditions may be an offence: see subsection 41MN(3).

(3) An exemption under paragraph (1)(a) has effect only for classes of persons prescribed in the regulations for the purposes of this subsection.

(4) If the regulations revoke an exemption, the revocation takes effect on the day specified. The day must not be earlier than 20 working days after the day on which the regulations are made.

Part 4-8 – Obtaining Information

Division 2 – Information relating to medical devices covered by exemptions

41JD Secretary may require information etc. about devices exempted under section 41HA from inclusion in the Register

(1) The Secretary may give the sponsor of kinds of medical devices exempted under subsection 41HA(1) from Division 3 of Part 4-11, a written notice requiring the sponsor to give the Secretary specified information or documents relating to one or more of the following:
   (a) the supply of devices of those kinds;
   (b) the handling of devices of those kinds;
   (c) the monitoring of the supply of devices of those kinds;
   (d) the results of the supply of devices of those kinds;
   (e) any other matter prescribed by the regulations for the purposes of this paragraph in relation to devices of those kinds.

(2) [Relates to Category A SAS]

(3) A notice under this section must specify a reasonable period within which the person must comply. The period must be at least 10 working days starting on the day on which the notice is given.

The Medical Devices Regulations:

Part 7 Exempting medical devices from inclusion in the Register

Division 7.1 Exempt devices

7.1 Exempt goods – general (Act s 41HA)

(1) For paragraph 41HA(1)(b) of the Act, a kind of medical device mentioned in Part 1 of Schedule 4 is exempt from the operation of Division 3 of Part 4-11 of the Act.

(2) For paragraph 41HA(1)(b) and subsection 41HA(2) of the Act, a kind of medical device mentioned in column 2 of an item in Part 2 of Schedule 4 is exempt from the operation of Division 3 of Part 4-11 of the Act, subject to compliance with the conditions mentioned in column 3 of that item.

(3) If:
(a) a kind of medical device that is exempt from the operation of Division 3 of Part 4-11 of the Act ceases to be so exempt; and
(b) an application was made for the kind of device to be included in the Register before the device ceased to be exempt;
the kind of device is taken to be exempt from the operation of Division 3 of Part 4-11 of the Act until the application is determined.

Schedule 4 Exempt devices (excerpt)

Part 2 Exempt devices – exemption subject to conditions

Item	Kinds of medical devices	Conditions
2.3	Medical device to be used solely for experimental purposes in humans	(a) Before starting to use the device, the sponsor must notify the Secretary: (i) in a form approved by the Secretary; and (ii) in accordance with any requirements determined by the Secretary for the form of notification; that the sponsor intends to sponsor a clinical trial using the device; (b) The notification must be accompanied by the relevant notification fee referred to in item 1.8 of Schedule 5; (c) The approval of the device for this purpose must be given by the sponsor (if the sponsor is conducting the trial), or by the body or organisation conducting the trial for the sponsor, having regard to the advice of the ethics

committee that has, or will assume, responsibility for monitoring the conduct of the trial;

(d) The terms of the approval by the sponsor, body or organisation referred to in paragraph (c) must be no less restrictive than the terms advised by the responsible ethics committee;

(e) The trial must not be the subject of a direction by the Secretary that the trial not be conducted, or that it be stopped, because the Secretary has become aware that to conduct or continue the trial would be contrary to the public interest;

(f) The sponsor (if the sponsor is conducting the trial), or the body or organisation conducting the trial for the sponsor, must not receive, or have received, advice from the responsible ethics committee that is inconsistent with the continuation of the trial.

(g) The conditions set out in regulation 7.5 must be complied with, as if that regulation applied to a person using a medical device under this item.

· **CTX Scheme Legal Arrangements**

The Act:

41HB Exemptions for special and experimental uses

(1) The Secretary may grant a written approval to a person for:
(a) the importation into Australia; or
(b) the exportation from Australia; or
(c) the supply in Australia;
of a specified medical device or kind of medical device (other than medical devices included in the Register or exempt devices):
(d) for use in the treatment of another person; or
(e) for use solely for experimental purposes in humans.

(2) The approval may be given subject to conditions specified in the approval, including a condition relating to charging for medical devices of the kinds in question.

Note: Breach of the conditions may be an offence: see subsection 41MN(3).

(3) In addition, the regulations may prescribe conditions that apply to a person's approval to use specified kinds of medical devices solely for experimental purposes in humans. The conditions may relate to one or more of the following:

(a) the preconditions on another person's use of devices of those kinds for these purposes;

(b) the principles to be followed in another person's use of devices of those kinds for these purposes;

(c) the monitoring of another person's use, and the results of that use, of devices of those kinds for those purposes;

(d) the circumstances in which that other person must cease using devices of those kinds of those purposes.

(4) An application to use specified medical devices in the treatment of another person must be accompanied by an information about the devices that is required by the Secretary.

(5) An application to use specified kinds of medical devices solely for experimental purposes in humans must:

(a) be made in writing; and

(b) be accompanied by any information about the kinds of devices that is required by the Secretary; and

(c) be accompanied by the prescribed fee.

(6) The Secretary must:

(a) consider any application under this section; and

(b) assess any information submitted with the application; and

(c) notify the applicant, within 20 working days of making the decision:

(i) of the decision; and

(ii) in the case of a decision not to grant the approval – of the reasons for the decision.

(7) The use by a person for experimental purposes in humans of specified kinds of medical devices that are the subject of an approval granted to someone else under paragraph (1)(e) is subject to the conditions (if any) specified in the regulations relating to one or more of the following:

(d) the preconditions on the use of devices of those kinds for those purposes;

(e) the principles to be followed in the use of devices of those kinds for those purposes;

(f) the monitoring of the use, and the results of the use, of devices of those kinds for those purposes;

(g) the circumstances in which the person must cease the use of devices of those kinds for those purposes.

Note: Breach of the conditions may be an offence: see subsection 41MN(3).

41JE Secretary may require information relating to approvals under section 41HB

Approval under subsection 41HB(1)

(1) The Secretary may give to a person granted an approval under subsection 41HB(1) (special and experimental uses), in relation to specified kinds of medical devices, a written notice requiring the person to give to the Secretary specified information or documents relating to one or more or more of the following:
   (a) the supply of devices of those kinds;
   (b) the handling of devices of those kinds;
   (c) the monitoring of the supply of devices of those kinds;
   (d) the results of the supply of devices of those kinds;
   (e) any other matter prescribed by the regulations for the purposes of this paragraph in relation to devices of those kinds.

Approval under subsection 41 HB(1) – use by another person

(2) The Secretary may give to a person using specified kinds of medical devices, that are the subject of an approval granted to someone else under paragraph 41HB(1)(e) (use solely for experimental purposes in humans), a written notice requiring the person to give to the Secretary specified information or documents relating to either of both of the following:
   (a) the use of devices of those kinds;
   (b) any other matter prescribed in the regulations for the purposes of this paragraph in relation to devices of those kinds.

Compliance period

(3) A notice under this section must specify a reasonable period within which the person to whom the notice is given must comply. The period must be at least 10 working days starting on the day on which the notice is given.

The Medical Devices Regulations:

Division 7.2 Exemptions for experimental uses

7.3 Conditions of approval – use of device by person to whom approval is given (Act s 41HB)

(1) For subsection 41HB of the Act, the condition mentioned in this regulation apply to an approval granted to a person to use a kind of medical device solely for experimental purposes in humans.

(2) Before the commencement of any clinical trial proposed to be undertaken in relation to the device, the person to whom the approval is granted and the principal investigator of the clinical trail must give to the National Manager of the Therapeutic Goods Administration:
   (a) a written assurance that each clinical trial will be conducted in accordance with the 'National Statement on Ethical Conduct in Research

Involving Humans', published by the National Health and Medical Research Council, as in force from time to time, and

(b) a written undertaking:

(i) that the person will comply with any request by an authorised person, whether made before of after the commencement of a clinical trial, to give to the authorised person information about the conduct of the trial; and

(ii) that the person will allow an authorised person to do any of the things mentioned in regulation 7.4 in relation to a clinical trial.

7.4 Powers of authorised persons in relation to medical devices being used in clinical trials

(1) For paragraph 7.3(2)(b)(ii) and subject to subregulation (2), an authorised person may do any of the following things in relation to a clinical trial of a kind of medical device that has been approved for use solely for experimental purposes in humans:

(a) enter the site of the trial;

(b) search the site and anything on the site;

(c) inspect, examine, take measurements of, or conduct tests on (including by the taking of samples), anything on the site that relates to the trial;

(d) take photographs, make video recordings or make sketches of the site or anything on the site;

(e) inspect any book, record or other document on the site that relates to the trial;

(f) request the principle investigator of the trial to:

(i) answer any question asked by the authorised person; or

(ii) produce any book, record or other document requested by the authorised person.

(2) An authorised person is not entitled to do a thing mentioned in subregulation (1) if:

(a) the principal investigator, or any other person present at the site concerned and in apparent control, requests the authorised person to produce his or her identity card for inspection; and

(b) the authorised person fails to comply with the request.

Note: See section 52 of the Act in relation to identity cards.

(3) The principal investigator, or any other person present at the site and in apparent control, is entitled to observe a search conducted under paragraph (1)(b), but must not obstruct the search.

(4) Subregulation (3) does not prevent 2 or more areas of the site being searched at the same time.

7.5 Conditions of approval – use of device by another person (Act s 41HB)

(1) For subsection 41HB(7) of the Act, the conditions mentioned in this regulation apply to the use by a person for experimental purposes in humans of a kind of medical device that is the subject of an approval granted to someone else under paragraph 41 HA(1) of the Act.

(2) The use of the device must comply with a procedural protocol approved by the ethics committee that is to be responsible for monitoring the conduct of the trial at each trial site (the ***responsible ethics committee***).

(3) The use of the device must be in accordance with the ethical standards set out in the 'National Statement on Ethical Conduct in Research Involving Humans', published by the National Health and Medical Research Council, as in force from time to time.

(4) The person must cease using the device if the responsible ethics committee informs the principal investigator of the clinical trial that the use is inconsistent with:
   (a) the protocol mentioned in subregulation (2); or
   (b) any condition subject to which approval for the use was given.

Act and Regulations Governing the Manufacture of Medicines for Use in Clinical Trials

Manufacturing of medicines is covered under Part 3.3 of the *Therapeutic Goods Act 1989*. Section 35 of the Act requires that medicines used in Australia must be manufactured by persons licensed to manufacture, or carry out a step in the manufacture, of medicines at licensed premises unless either the goods or person are exempt in relation to the manufacture of therapeutic goods. Also, manufacturers of medicines are required to comply with written manufacturing principles under Section 36 of the *Therapeutic Goods Act* 1989. In Australia, these principles include the *Australian Code of Good Manufacturing Practice for Medicinal Products, 16 August 2002*, as adopted by the TGA.

Some of the production processes of investigational medicinal products may be different to those required for a routine production operation. Such products may not be manufactured under a set routine and may possibly, at the initial stages of development, have incomplete characterisation. The product specifications and manufacturing instructions may vary during development, resulting in increased complexity of the manufacturing operation.

Annex 13 of the *Australian Code of Good Manufacturing Practice for Medicinal Products – Manufacture of Investigational Medicinal Products*, specifically deals with those aspects of Good Manufacturing Practice that may be different for investigational medicinal products. The annex provides guidance for investigational medicinal products at all stages of development. In particular, it should be used as the basis for licensing of manufacture of clinical trials materials that are used beyond the initial clinical studies in human volunteers.

Note: Annex 13 of the *Rules Governing Medicinal Products in the EU, Volume 4, Good Manufacturing Practices* was revoked in August 2002 and replaced by Annex 13 of the *Australian Code of Good Manufacturing Practice for Medicinal Products, 16 August 2002*. This was promulgated by Therapeutic Goods (Manufacturing Principles) Determination No. 1 2002.

Medicines used in initial experimental studies in human volunteers, ie, most Phase I studies of medicines are exempted from the operation of Part 4 of the Act under Schedule 7 of the *Medicines Regulations*, pursuant to Section 34(1) of the Act and Regulation 17 of the Regulations. The exemption would also apply to medical device trials where the studies are concerned with design and prototype development. No such exemption exists for therapeutic goods used in other phase studies. In the case of investigational medicinal products, the manufacturing processes should at least comply with Annex 13 of the *Australian Code of Good Manufacturing Practice for Medicinal Products – Manufacture of Investigational Medicinal Products.*

Summary of specific provisions in the Act and Regulations

The Act:

34 Exempt goods and exempt persons

(1) The regulations may exempt therapeutic goods or a class of therapeutic goods identified in the regulations from the operation of this Part.

[(2) - (3) Unrelated to clinical trials]

36 Manufacturing principles

(1) The Minister may, from time to time, determine written principles to be observed in the manufacture of therapeutic goods for use in humans.

(2) The manufacturing principles may relate to:

(a) the standards to be maintained, and the equipment to be used, at premises used for the manufacturing of therapeutic goods for use in humans; or

(b) procedures for quality assurance and quality control to be employed in the manufacturing of therapeutic goods for use in humans; or

(c) the qualifications and experience required of persons employed in the manufacture of therapeutic goods for use in humans; or

(d) the manufacturing practices to be employed in the manufacturing of therapeutic goods for use in humans; or

(e) other matters relevant to the quality, safety and efficacy of therapeutic goods for use in humans that are manufactured in Australia;

and may include codes of good manufacturing practice.

(3) The minister may, before taking action under subsection (1) in relation to manufacturing principles, obtain advice from a committee established by the regulations on the action that should be taken under that subsection as to the principles to be observed in the manufacture of therapeutic goods for use in humans.

(4) Manufacturing principles are disallowable instruments for the purposes of section 46A of the *Acts Interpretation Act 1901*.

The Regulations:

17 Exempt goods for the purposes of subsection 34 (1) of the Act

(1) For the purposes of subsection 34 (1) of the Act, the therapeutic goods specified in Schedule 7 are exempt from the operation of Part 4 of the Act unless the goods are supplied as pharmaceutical benefits.

(2) If:

(a) therapeutic goods that are exempt from the operation of Part 4 of the Act cease to be exempt; and

(b) before the day on which the goods cease to be exempt, each person who carries out a step in the manufacture of the goods applies for a licence authorising the person to carry out a step on the premises referred to in the application;

the goods produced by those persons carrying out the steps on those premises are taken to be exempt from the operation of that Part of the Act until each application is determined.

Schedule 7 (excerpt)

Column 1	Column 2
Item	Therapeutic goods
1	goods prepared for the initial experimental studies in human volunteers

Points of note in relation to the manufacture of clinical trial medicines

The following clauses are guidelines dealing with packaging, labelling, randomisation, blinding, shipping and returns have been reproduced from Annex 13 of the *Australian Code of Good Manufacturing Practice for Medicinal Products – Manufacture of Investigational Medicinal Products*, with their clause numbers for convenience. Note: this is not to imply that manufacturers of clinical trial material should not comply with the remaining clauses of the Annex.

A copy of Annex 13 of the *Australian Code of Good Manufacturing Practice for Medicinal Products – Manufacture of Investigational Medicinal Products* can be found on the TGA website at:

http://www.tga.gov.au/pdf/archive/manuf-medicines-cgmp-020816.pdf

· **Packaging instructions**

14. Packaging and labelling of investigational medicinal products are likely to be more complex and more liable to errors (which are also harder to detect) than of marketed products when "blinded" labels are used. Supervision procedures such as label reconciliation, line clearance, etc. and the independent checks by quality control staff should accordingly be intensified.

15. Investigational medicinal products must be packed in an individual way for each patient included in the clinical trial. Packaging instructions are based on the order. Contrary to what happens with large-scale manufacturing of licensed medicinal products, batches of investigational medicinal products may be subdivided into different packaging batches and packaged in several operations over a period of time.

16. The number of units to package should be specified prior to the start of the packaging operations, considering also the number of units necessary for carrying out quality controls and the number of samples to be kept. A reconciliation should take place at the end of the packaging and labelling process.

· **Labelling instructions**

17. Labels should include:
    a) name of the sponsor;
    b) pharmaceutical dosage form, route of administration, quantity of dosage units (and name/identifier of the product and strength/potency in case of open trial);
    c) the batch and/or code number to identify the contents and packaging operation;
    d) the trial subject identification number, where applicable;

e) directions for use;
f) "for clinical trial use only";
g) the name of the investigator (if not included as a code in the trial reference code);
h) a trial reference code allowing identification of the trial site and investigator;
i) the storage conditions;
j) the period of use (use-by date, expiry date or re-test date as applicable), in month/year);
k) "keep out of reach of children" except when the product is for use only in hospital;

The outer packaging may include symbols or pictograms to clarify certain information mentioned above and the request "return empty packaging and unused products".

Additional information, for example any warnings and handling instructions, where applicable, may be displayed according to the order. A copy of each type of label should be kept in the batch record.

18. On the immediate packaging when the outer packaging carries the particulars mentioned in paragraph 17 a-k, the particulars mentioned in paragraph 17 a-f, shall be given.

19. When the outer packaging carries the particulars mentioned in paragraph 17 a-k and the immediate packaging takes the form of blister packs or small immediate packaging units such as ampoules on which the particulars mentioned in paragraph 17 a-f can not be displayed, the particulars mentioned in paragraph 17 a, c and d as well as route of administration in case of ampoules, shall at least appear on the immediate packaging.

20. In case of use date extension, an additional label should be affixed to the investigational medicinal product. This additional label should include the new use date and repeat the batch number. It may be superposed on the old use date, but, for quality control reasons, not on the original batch number. This operation may be performed on site by the clinical trial monitor(s) or the clinical trial site pharmacist, in accordance with specific and standard operating procedures and under contract if applicable. The operation should be checked by a second person. Documented evidence of this additional labelling should be available in the trial documentation and in the batch records.

Labelling of clinical trial medicines - TGA comments

In the case of trials involving more than one Australian site, the trial reference code [paragraph 17(h) of Annex 13] need only allow identification of the principal Australian trial site and the principal Australian investigator. If the name of the principal Australian investigator is not included as a code in the trial reference code, then the name of the principal Australian investigator should appear on the label [paragraph 17(g) of Annex 13]. The principal Australian trial site should keep adequate records of drug distribution.

The name of the Australian sponsor should appear on the label [paragraph 17(a) of Annex 13]. The Australian sponsor is the company or individual who signs the CTX or CTN application and takes overall responsibility for the conduct of the trial in Australia. It is not sufficient to include only an overseas sponsor name in the case of a multinational trial.

The TGA does not allow labels to omit an expiry or re-test date. Annex 13 provides comprehensive guidance on 'use date extension', and the TGA expects sponsors to comply with that guidance.

The labelling requirements of Annex 13, taking the above comments into account, is summarised in the following table. All requirements are to be included on the outer packaging of the drug product. Information to be included on the immediate container is shown in the following table.

Requirement	Required on immediate container?	Comments
Name of sponsor	44	must be the Australian sponsor
Trial reference code		must allow identification of the principal Australian trial site
Batch no.	44	may be encoded for blinding purposes
Subject identification no.	44	'where applicable'
Storage conditions		those of TGO48* preferred by the TGA
Expiry date (month/year)		may be replaced by a re-test date
Dosage form	4	
Route of administration	4	must be present on ampoule labels, even if the ampoule is small
Quantity of dosage units	4	
Directions for use	4	
"for clinical trial use only"	4	
Name of the investigator		must be the principal Australian investigator, and may be included as a code within the trial reference code
"keep out of reach of children"		not required when product is for use only in hospital
Drug name and potency	4	for open trials only

4 Must be present on immediate pack, except for blister packs or small immediate packaging units such as ampoules
44 Must be present on all immediate packs

* TGO48 – Therapeutic Goods Order No 48 "General requirements for labels for drug products". 1994

· **Randomisation code**

29. Procedures should describe the generation, distribution, handling and retention of any randomisation code used for packaging investigational products.

· **Blinding operations**

30. A system should be implemented to allow for a proper identification of the 'blinded' products. The system, together with the randomisation code and randomisation list must allow proper identification of the product, including any

necessary traceability to the codes and batch number of the product before the blinding operation.

31. Samples of blinded investigational medicinal products should be retained.

· **Shipping – Returns – Destruction**

40. Shipping, return and destruction of unused products should be carried out according to written procedures.

Shipping

41. Shipping of investigational products is conducted according to orders given by the sponsor in the shipping order.

42. Investigational medicinal products are sent to an investigator only after a two step release procedure: the release of the product after quality control ('technical green light') and the authorization to use the product, given by the sponsor ('regulatory green light'). Both releases should be recorded and retained.

43. The packaging must ensure that the medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

44. The sponsor should ensure that the shipment is to be received in the required conditions and acknowledged by the right addressee.

45. A detailed inventory of the shipments made by the manufacturer should be maintained. It should particularly mention the addressees' identification.

46. Transfers of investigational medicinal products from one trial site to another should remain the exception and only be allowed in case of very expensive product, limited quantity available for clinical trials or in case of emergency. Such transfers should be covered by standard operating procedures which differentiate between the storage location of the product to be transferred (from warehouse under control of the sponsor, from the pharmacy of a trial site, or from the investigator). Should the transferred product have been stored by the investigator, not at the pharmacy, sufficient precautions and controls have to be considered prior to use at an other trial site. In most cases, the product will need to be returned to the sponsor for re-labelling and full finished product specification retesting to ensure that it is still suitable for its intended use and new release.

Returns

47. Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in written procedures, and approved by authorised staff members.

48. Returned investigational medicinal products should be clearly identified and stored in a dedicated area. Inventory records of the returned medicinal products should be kept.

Destruction

49. The Sponsor is responsible for the destruction of unused investigational medicinal products. Investigational medicinal products should therefore not be destroyed by the manufacturer without prior written authorisation by the sponsor.

50. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The records should be kept by the sponsor. This destruction should be done only after the finalisation of the clinical trial and the compilation of the final report.

51. If the manufacturer is requested to destroy the products, he should deliver a certificate of destruction or a receipt for destruction to the sponsor. These documents should clearly identify the batches and/or patient numbers involved and the actual quantities destroyed.

Act and Regulations Governing the Manufacture of Medical Devices for Use in Clinical Trials

Manufacturing of medical devices is covered under Part 4-3 of the *Therapeutic Goods Act 1989*. This part of the Act deals with Conformity Assessment Procedures, which set out the general requirements relating to the application of quality management systems for the manufacture of medical devices for marketing in Australia. The requirements are prescribed in Division 3 of the medical devices Regulations and Schedule 3 to those regulations.

There are no specific requirements prescribed in the medical device Regulations for the manufacture of medical devices for use in clinical trials. However, there is an expectation that the manufacturer will have documented elements of a quality management system (eg a Plant Master File for the manufacturing site) as well as technical information to demonstrate compliance with the essential principles for performance and safety as far as practical for the stage of development of the device. The quality management system for a medical device in the initial stages of development will not have necessarily undergone independent review, assessment and certification by a notified body or the TGA at that point in time. However, medical devices that are in the final form, suitable for release onto the market, are expected to be supported by evidence of quality management system certification. The intention is that the manufacturer is able to demonstrate that they are able to manufacture the device consistently and that the design and function of the device under investigation are well characterised. As a general guide, the technical documentation held by the manufacturer should include:

- a general description of the device;
- drawings of the design of the device, including components, subassemblies or circuits;
- descriptions or explanations that are necessary to understand either the drawings of the device or its intended purpose;
- a description of any sterilisation processes used in the manufacture of the device;
- details of any standards used in relation to the manufacture of the device;
- design calculations, risk analyses and technical tests or any other investigations carried out on the device;
- where the device is to be used in conjunction with (eg connected to) other devices, results of tests demonstrating the safety and performance of each device is acceptable; and
- a copy of the information to be provided with the device.

Sponsors of clinical trials of unapproved medical devices should, as far as practical, ensure that the device complies with the essential principles for performance and safety as described in the Schedule 1 of the medical device Regulations.

There is no document available at present that specifically deals with issues relating to the manufacture of investigational medical devices. However, many of the principles outlined in Annex 13 of the *Australian Code of Good Manufacturing Practice for Medicinal Product* have relevance to medical devices as well.

Summary of specific provisions in the Act and Regulations

· ***The Act***

41D What this Part is about

The conformity assessment procedures set out the requirements relating to the application of quality management systems for medical devices, and other requirements imposed on manufacturers. Compliance with applicable conformity assessment standards is not required, but it is one way to establish that one or more parts of the conformity assessment procedures have been applied to medical devices.

Division 1 – Conformity assessment procedures

41DA Conformity assessment procedures

(1) The regulations may set out requirements relating to the obligations of manufacturers of medical devices.

(2) These requirements are to be known as the ***conformity assessment procedures***.

(3) The conformity assessment procedures, or any part of the conformity assessment procedures, may:
- (a) be limited in their application to one or more medical device classifications; or
- (b) apply differently to different medical device classifications, different kinds of medical devices or different manufacturers

(4) Without limiting subsection (1), the regulations may relate to all or any of the following:
- (a) application of quality management systems for the manufacture of medical devices;
- (b) certification of compliance with the essential principles, or the quality management systems for the manufacture of medical devices;
- (c) notification of, and assessment of, changes to a manufacturer's product range, product design or quality management systems;
- (d) declarations to be made by manufacturers of medical devices that conformity assessment procedures have been applied to the devices;
- (e) marks to be affixed to medical devices indicating the application of the conformity assessment procedures to the devices;
- (f) monitoring and inspecting the design of medical devices or the manufacturing processes for medical devices;
- (g) monitoring the performance of medical devices;
- (h) corrective action required in relation to the design, manufacture, packaging, labelling and supply of medical devices;

(i) keeping records of the manufacture of medical devices, the design of medical devices or the manufacturing processes for medical devices.

· ***The medical devices Regulations***

3.10 Medical devices used for a special purpose

(1) this regulation applies to the following kinds of medical devices (***medical devices used for a special purpose***):
(a) an exempt device;
(b) a medical device that is the subject of an approval under section 41HB of the Act;
(c) [relates to Authorised Prescribers]
(d) [relates to procedure packs]

Note for paragraph (a) An ***exempt device*** is a medical device of a kind that is exempted from the Operation of Division 3 of Part 4-11 of the Act by the regulations (see subsection 3(1) of the Act). Division 7.1 and Schedule 4 of these Regulations deal with exempt devices

(2) The conformity assessment procedures that must be applied to a medical device used for a special purpose are the procedures for medical devices used for a special purpose.

(3) [Relates to procedure packs]

(4) [Relates to procedure packs]

Schedule 3 Conformity Assessment Procedures

Part 7 Procedures for medical devices used for a special purpose

7.1 Overview

The conformity assessment procedures set out in this Part provide for the manufacturer of a medical device used for a special purpose:
(a) to prepare a written statement containing certain information in relation to the device; and
(b) to prepare and keep up-to-date particular documentation in relation to the device.

Note: The procedures cover custom-made medical devices (7.2) and system or procedure packs (7.5). There are no requirements specifically relating to medical devices used in clinical trials.

Release of Information

Information provided to the TGA concerning the use of unapproved therapeutic goods in relation to clinical trials will be treated as confidential within the constraints of Section 61 of the *Therapeutic Goods Act 1989* which prescribes certain circumstances in which information may be released.

The *Freedom of Information Act 1982* (FOl Act) also governs access to information. Section 27 of the FOI Act requires that consultation occur between the TGA and the owner of the information prior to release of that documentation.

In addition, the *Privacy Act 1988* places limits on the disclosure of personal information by parties in possession or control of records. Such parties cannot disclose personal information about an individual to a person, body or agency other than the individual concerned except under certain circumstances. This include situations where:

- the individual concerned has consented to the disclosure or is reasonably likely to have been aware that information of that kind is usually passed to that person, body or agency;
- the holder of the record has reasonable grounds to believe that disclosure is necessary to prevent or lessen a serious, imminent threat to life or health of the individual concerned;
- the disclosure is required or authorised by or under law; or
- the disclosure is reasonably necessary for the enforcement of criminal law or of a law imposing criminal penalty, or for the protection of the public revenue.

Therefore information supplied to the TGA maybe released in circumstances consistent with the Privacy and FOI legislation.

Under the *Therapeutic Goods Act 1989*, the TGA is also able to release information concerning the use of unregistered therapeutic goods to State and Territory authorities, which have a need to know. This allows States and Territories to have information to take action on matters under their jurisdiction, such as medical or pharmacy practice. The circumstances under which this may occur include, but is not limited to, the TGA becoming aware that a medical practitioner is using notification mechanisms (eg Category A SAS or the CTN Scheme) inappropriately so as to avoid having to obtain approval from the TGA for supply of an unapproved therapeutic good or where audit of a clinical trial establishes issues of negligent or unprofessional behaviour.

Doctors and sponsors reporting adverse events associated with use of unapproved products to the TGA should be familiar with and discharge obligations in relation to the collection, use and disclosure of personal information in accordance with the National Privacy Principles based on the *Privacy Act 1988*. These obligations are set out in the *Guidelines on Privacy in the Private Health Sector, Office of the Federal Privacy Commissioner, November 2001*. The TGA's requirement for applicants to provide information on an identifiable patient does not override these privacy principles and explicit consent to the disclosure of the patient's identity to TGA must be sought.

Importation restrictions

The *Therapeutic Goods Act 1989* prohibits the importation or supply of unapproved therapeutic goods for use in humans unless they are exempted. Item 1 of Schedule 5A of the Regulations and Item 2.1 of Schedule 4 of the medical devices Regulations allows for the importation of unapproved products under Sections 18, 19, 41HA, 41HB or 41HC of the Act, but they must be stored and not supplied for use in humans until that approval or notification is finalised.

Importation of a products for an unapproved use or as part of a clinical trial may be subject to additional restrictions for which additional and separate approvals may be required under legislation governing:

- the *Customs (Prohibited Imports) Regulations* (for example, products containing abortifacients, antibiotics, anabolic steroids, growth hormones, narcotics, psychotropic medicines and certain prohibited substances);
- the *Quarantine Act 1908* (for example, materials of biological origin);
- the *Wildlife Protection (Regulation of Imports and Exports) Act 1982* (for example, products originating from endangered species); and
- current arrangements for the prior approval of clinical investigations involving genetically modified materials.

THE CLINICAL TRIAL NOTIFICATION (CTN) SCHEME

Introduction

This section should be read in conjunction with the introductory section to this document which outlines circumstances under which clinical trials are regulated under either the CTN or CTX Schemes, as well as which scheme may be more appropriate to the context in which the study is being conducted. The procedures and administrative requirements outlined in this section apply to clinical trials of medicines and medical devices.

The Clinical Trial Notification Scheme (CTN) is designed to combine rapid approval of clinical trial protocols with ongoing monitoring and supervision by HRECs acting in accordance with nationally agreed guidelines developed by the NHMRC. Under the CTN Scheme, a proposal to conduct the trial at each trial site is submitted directly to the HREC responsible for the site by the principal investigator, on behalf of the sponsor. The TGA does not review any data relating to the clinical trial. The HREC is responsible for assessing the scientific and ethical validity of the trial, and the safety and efficacy of the medicine in the context of the phase of development of the medicine. In some institutions a scientific review or drug subcommittee may review the application before consideration by the HREC.

The Clinical Trial Notification Procedure

The investigator is required to submit a research proposal to the HREC. The proposal would normally include the protocol, the investigator's brochure, related patient information, supporting data and the CTN form (**Appendix 2**). HRECs usually have their own standard format for applications to conduct a clinical trial at their institution.

The HREC is responsible for approving the protocol for the clinical trial. The institution or organisation at which the trial will be conducted, referred to as the "Approving Authority", gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC. The person responsible on behalf of the Approving Authority must sign the CTN Form. In some cases the HREC can also be the Approving Authority for a particular trial site. The same person can sign the CTN Form on behalf of the HREC and the Approving Authority, but they should indicate the position or capacity in each instance. Also, the same person may sign the CTN Form on behalf of the sponsor and the Approving Authority. However, because of the potential for conflict of interest, the same person cannot sign on behalf of the HREC and the principal investigator, nor can they sign on behalf of the sponsor of the trial and the HREC.

Once the sponsor, the principal investigator, the Chairman of the HREC and the person responsible from the Approving Authority have signed the CTN Form, it is submitted to the TGA with the notification fee. A CTN trial must be notified to the TGA before it can commence.

A clinical trial is deemed to have been notified as soon as the requirements set out under Item 3 of Schedule 5A of the Regulations or Item 2.3 of Schedule 4 of the medical devices Regulations have been met (ie completion of the CTN form and forwarding it and the relevant fee to the TGA). Once this occurs the exemption comes into effect and the sponsor can supply the goods. Waiting for an acknowledgement from the TGA is not one of the

requirements. Thus, a sponsor does not have to wait for the TGA's acknowledgement letter before commencing the trial. However, it is advisable for sponsors to wait for the TGA's acknowledgement in case there is anything, such as incomplete information on the CTN form that might invalidate the notification. It should be noted that The Therapeutic Goods Regulations require notification to be in a 'form' approved by the Secretary of the Department of Health and Ageing. It is essential that the current CTN form is used to notify trials. Use of old (out-of-date) CTN forms will invalidate the notification.

There must be one Clinical Trial Notification Form for each site conducting the same clinical trial. Thus, for multicentre trials, there is one CTN Form for each site.

In some instances, it may be possible to notify a trial as a composite site trial if a single ethics committee and approving authority has appropriate authority for all sites participating in the trial. For example, a GP-based trial conducted by a general practice network may be notified as a composite site trial.

Extension of Clinical Trial Programs

The sponsor may seek approval of an HREC to conduct further trials with the same product. In each case, the sponsor of the trial is required to submit a further CTN Form to the TGA. A clinical trial program initially approved under the CTX Scheme may also be extended beyond the approved Usage Guidelines by notification under the CTN Scheme.

All parties involved in the planning, approval and conduct of clinical trials that involve the use of unmarketed products should consider mechanisms for access to continued treatment with those unmarketed products by patients for whom treatment has been found to be effective and where long term therapy would be appropriate following completion of the trial. Parties should therefore consider including a post study supply component in the research protocol.

Information Required by TGA on Completion of the Trial

The TGA maintains a record of each CTN trial and each trial site conducting a trial under the CTN application. To maintain the record for each trial, the TGA must be notified of:

- the date the trial was completed (ie last date of completion for all sites. It is not necessary to notify completion dates for individual sites);
- the reason the trial ceased (eg concluded normally; insufficient recruits etc); and
- any changes to the trial in respect of information previously submitted to TGA.

The information contained under the first two dot points above can be notified to the TGA using a *Clinical Trial Completion Advice - CTN and CTX Schemes* form. A copy of this form can be found in **Appendix 3**.

Administrative requirements

Address for notifications

The 'Notification of Intent to Conduct a Clinical Trial' form and a cheque for the notification fee should be sent by post or courier to:

The Business Management Unit
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
Australia

Fees

A notification fee is payable for each notification under the CTN Scheme. Processing of a notification will not commence until the notification fee is paid. The level of fees is set out in Schedule 9 of the Regulations and Schedule 5 of the medical devices Regulations and a summary of the current schedule of fees may be obtained from the TGA Information Officer (phone 1800 020 653) or is available on the TGA's Internet website (www.tga.gov.au).

The fee for each act of notification pertaining to the conduct of a clinical trial under the CTN Scheme is set out in the Regulations. If there is more than one body or organisation involved in the same CTN protocol, the sites involved in the clinical trial can be notified in a number of ways:

All sites notified at same time: Single CTN fee
(includes composite site)
Each site notified individually: CTN fee is payable for each separate notification
Sites notified in groups: CTN fee is payable for notification of each group

CLINICAL TRIAL EXEMPTION (CTX) SCHEME

Introduction

This section should be read in conjunction with the introductory section to this document which outlines circumstances under which clinical trials are regulated under either the CTN or CTX Schemes, as well as which scheme may be more appropriate to the context in which the study is being conducted.

Supply of unapproved products under the CTX Scheme requires the approval of the Secretary of the Department of Health and Ageing. In practice, the supply of the goods under the CTX Scheme can occur if no objection to the conduct of the clinical trial is raised by the TGA within certain agreed timeframes (see below). The scheme mirrors the scheme in place for the regulation of clinical trials of medicines in the UK. More information about the UK CTX Scheme can be obtained from the UK Medicines and Healthcare products Regulatory Agency (MHRA) website:

http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/clintrials.htm#CTX

A CTX application offers sponsors the opportunity of a review by the TGA of relevant, but limited, scientific data (which may be preclinical and early clinical data) prior to the commencement of the trial. This can be particularly useful for therapeutic goods that are in the early stages of development. Under the CTX Scheme, a number of trial protocols may be conducted under the one CTX application as long as they are all consistent with the approved Usage Guidelines.

A sponsor cannot commence a CTX trial until:

- written advice has been received from the TGA regarding the CTX application; and
- approval for the conduct of the trial has been obtained from an ethics committee and the institution at which the trial will be conducted.

There are two forms, each reflecting these separate processes (Parts), that must be submitted by the sponsor. Part 1 constitutes the formal CTX application. It must be completed by the sponsor of the trial and submitted to TGA with data for evaluation. Part 2 is used to notify the commencement of each new trial conducted under the CTX as well as new sites in ongoing CTX trials. These forms are located at **Appendix 4**.

The sponsor's interaction with TGA for trials conducted under a CTX, therefore, involves two steps. In the first step, the application is submitted to the TGA. The TGA evaluates the safety of the product and agrees to Usage Guidelines for the product which form the basis of any number of future trials. The second step is a notification step whereby, once HREC and Approving Authority approvals have been received by the principal investigator, the trial can commence on the condition that the sponsor of the trial notify the TGA within 28 days of commencing to supply the goods.

The notification, containing certifications of the sponsor, principal investigator, HREC and Approving Authority, is required to inform the TGA of the conduct of each specific trial and to demonstrate that all of the parties involved in the conduct of individual trials have complied with legislative and regulatory requirements and agree to release information to the

TGA about the conduct of the trial in the event of an inquiry or audit of the trial of the TGA. There is no fee for notification of trials under the CTX scheme.

The CTX Application Procedure

Under the CTX Scheme, a sponsor submits an application (CTX Part 1 form and accompanying data) to conduct clinical trials to the TGA for evaluation and comment. The TGA reviews summary information about the product, including adverse event data and information to be provided to HRECs by the sponsor, such as the overseas status of the product and proposed Usage Guidelines.

In the case of trials of medicines, the application should contain summaries of pharmaceutical data, preclinical data and clinical data. For medical device trials the TGA examines the summary reports on risk analysis, design specifications, manufacturing and materials, and preclinical and/or clinical data.

Conduct of a trial under the CTX Scheme must also be approved by the responsible HRECs. Applications can be lodged simultaneously with the TGA and the institution(s) at which studies are proposed to be conducted. If the application is lodged simultaneously with the TGA and HREC(s), the sponsor is required to convey any TGA comments or revisions on the application and/or objections to all the HREC(s).

The TGA Delegate decides whether or not to object to the proposed Usage Guidelines for the product. If an objection is raised, the trial may not proceed until the objection has been addressed to the Delegate's satisfaction. Even if no objection is raised, the Delegate usually provides comments on the accuracy or interpretation of the summary information supplied by the sponsor. The sponsor must forward these comments to the HREC(s).

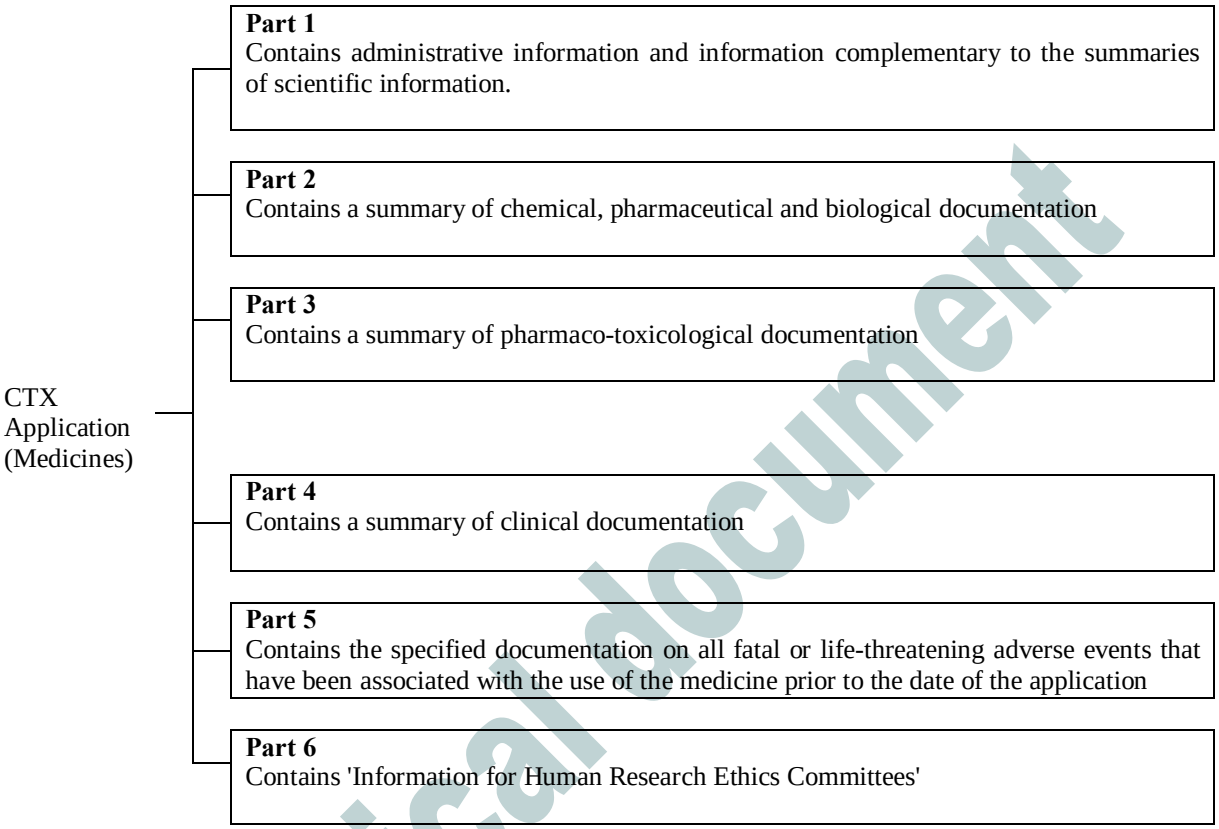
It is important to note that the application submitted to the TGA does not include the clinical trial protocol(s). The primary responsibility of the TGA is to review the safety of the product and the HREC is responsible for considering the scientific and ethical issues of the proposed clinical trial protocols.

The HREC in each host institution/organisation is responsible for approving the proposed trial protocol after reviewing the summary information received from the sponsor and any additional comments from the TGA Delegate. The institution or organisation concerned gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC. As noted previously, the institution or organisation is referred to as the "Approving Authority".

The sponsor may conduct further clinical trials without further assessment by the TGA, provided use of the medicine in the trials falls within the original approved Usage Guidelines. However, HREC approval of each protocol and approval from the institution/organisation for the conduct of the trial are still required.

CTX Application Format and Content for Clinical Trials of Medicines

Data submitted in support of a CTX application will be assessed by the TGA primarily in relation to safety. A CTX application should be presented in 6 parts. Four copies of the complete application are required to allow for simultaneous evaluation in different sections of the TGA.



A more detailed description of the content of each part of the clinical trial application is provided below:

- **Part 1** - Administrative information and information complementary to the summaries of scientific information.

  Part 1 provides a very brief overview of information complementary to the summaries of scientific information. It should contain any necessary covering letter or introduction, the application form (CTX Part 1, **Appendix 4**) and information under the heading 'Particulars of the Product and Trial' (**Appendix 5**). The formats shown in the above mentioned appendices should be used and each section should be completed. With respect to the 'Particulars of the Product and Trial', no reference should be made to data held elsewhere. The words ‘Not Applicable’ should be entered where appropriate.

- **Parts 2, 3 and 4** - Summaries of scientific data

  The general form of the summaries, as described below, corresponds to the form of the summaries currently required under the CTX Scheme in the UK. Summaries submitted to support a CTX application in the UK are acceptable for submission in this section, together with responses provided to any questions asked by the UK agency.

A declaration by a medical or scientific adviser to the sponsor is required, stating that the summaries are an accurate account of the data and that it is reasonable for the study to proceed.

The summaries will reflect the individual studies carried out by or on behalf of the sponsor, and studies in the published literature. A separate summary of each individual study may not be necessary if a series of related studies could be summarised together. Interpretative discussion of the scientific significance of the results of each study, or series of related studies, must be included. Tabular presentation is preferred when data from a number of studies are presented in a comparative way.

The degree of flexibility employed in data requirements is governed by the type of product, stage of development and the proposed clinical trials. The technical content of the summaries may be appropriately modified for specific cases, such as biological products, whilst following the general pattern.

General rather than comprehensive guidance is provided below. If the applicant is in doubt as to the data to support a specific application then advice should be sought from the Experimental Drugs Section within the DSEB.

· **Part 2** - Chemical, Pharmaceutical and Biological Documentation

A statement on the chemical structural formula must be given for each active constituent. Where the active constituent is the subject of a monograph, the monograph name may be given instead of the formula.

Summaries of the pharmaceutical data must be provided in respect of:

(a) the method of synthesis of each active constituent and the results of any physico-chemical tests, including legible copies of relevant spectra (IR, UV, NMR, MS etc) to substantiate the structure of the compound. Where the active constituent is the subject of a monograph the monograph name may be given instead of those data;

(b) the specification of each constituent (including control over impurities) whether active or excipient. Where a specification has not been established, a batch characterisation for each batch of that constituent to be used in the clinical trial should be provided. Where a constituent is the subject of a monograph, the monograph name may be given instead of the specification;

(c) in the case of each constituent, whether active or not, the quality control procedures and methods to be applied to ensure compliance with the specification;

(d) the method of manufacture or assembly of the medicinal product;

(e) the in-process specifications and methods employed to ensure quality and uniformity of each batch of the medicinal product;

(f) evidence of the stability of the medicinal product and of its bioavailability for the use intended;

(g) the finished product specifications and methods for determining the identity, purity and potency of the medicinal product. The address of the premises where such procedures are to be carried out;

(h) details as specified in (a) to (g) for comparator products and placebo products or an explanation of why such details have not been provided; and

(i) the sponsor should also provide an assurance that the clinical trial products have been manufactured in accordance with a therapeutic goods manufacturing licence (where such a licence is required in the country of manufacture) and in accordance with general principles of good manufacturing practice.

- **Part 3** - Pharmaco-Toxicological Documentation

The results of all available preclinical pharmacodynamic, pharmacokinetic and toxicological studies should be provided in summary form. The discussion should highlight the most important findings from the studies, including:

- nature, frequency and severity of pharmacological or toxic effects, including;
  - time of onset and duration;
  - reversibility;
  - dose response of observed effects and no observable effect level;
- importance of metabolites in regard to toxicity and therapeutic activity
- a summary of the pharmacokinetics, biological transformation and disposition of the investigational product in all species tested
- relevance of findings to humans

The discussion should include an assessment of the animal models used in the preclinical studies based on pharmacodynamic and pharmacokinetic results. Wherever possible, comparisons should be made in terms of systemic exposure rather than on a mg/kg basis. Tabular format/listings should be used whenever possible to enhance the clarity of presentation.

For clinical trials of 6 months duration or longer, the summary should contain a discussion of the carcinogenic potential of the investigational product.

- **Part 4** - Clinical Documentation

Summaries of reports and evaluations of any clinical studies carried out with each product or its constituents, which in the view of the sponsor are relevant to the assessment of safety, quality or efficacy of the medicinal product should be provided in this Part. References to relevant publications or other clinical trials should be included if relevant to the safety evaluation.

There is no formal requirement for prior studies in humans. However if any studies have been undertaken and they have any relevance to the drug's safety, they should be reported

in the summary. Detailed documentation of fatal or life-threatening adverse events should also be provided separately in Part 5 of the application.

- **Part 5** - Documentation of fatal or life-threatening adverse events

  Documentation of all reported fatal or life-threatening adverse events associated with the use of the drug prior to the date of the application should be included in this section. Relevant reports should be included from all countries in which the drug has been used. The Council for International Organisations of Medical Sciences (CIOMS) format is satisfactory for reports not originating in Australia.

  'Life-threatening' in this context means that 'the patient was, in the view of the investigator, at immediate risk of death from the event as it occurred' (ie. it does not include an event that had it occurred in a more serious form, might have caused death).

  'Associated with the use of the medicine' means that there is a reasonable possibility that the event may have been caused by the medicine.

  This documentation is in addition to the description of adverse events included in the summary of 'Clinical Documentation' where other adverse events will be identified and discussed.

  For details of reporting requirements for adverse events that occur during the period in which a trial is conducted under the CTX Scheme, for both adverse events in overseas countries and in Australia, refer to page 71 of this document.

- **Part 6** - Summary Information for Human Research Ethics Committees

  In order to assist the responsible HREC(s), sponsors of investigational medicines should prepare a separate section of summary information for HRECs. Information should include (but should not be limited to):

  - a summary statement (**Appendix 6, Document 1**);
  - the status of the medicine in overseas countries with similar regulatory procedures (**Appendix 6, Document 2**);
  - a summary data sheet on Chemical, Pharmaceutical and Biological documentation ;
  - a summary data sheet on Pharmaco-toxicological documentation ;
  - a summary data sheet on clinical documentation ;
  - usage guidelines (**Appendix 6, Document 3**).

  Summary data sheets should be prepared by the sponsor to summarise for HRECs the relevant scientific data to support the proposed trial. Separate headings should be used for chemical/ pharmaceutical or biological data, pharmaco-toxicological data and clinical data.

A recent (less than six months old) edition of the Investigator's Brochure may be submitted in place of the summary statement and summary data sheets. If this option is taken, it is important to append a safety update if there have been any significant events since the Investigator's Brochure was prepared.

The status of the medicine in overseas countries can include both marketing and clinical trial status.

The Usage Guidelines are a key document in the CTX application. These describe the boundaries of the proposed use of the product, such that further trials that are consistent with the Usage Guidelines can be conducted without further TGA approval (except for significant changes to chemistry/pharmaceutical aspects of the product - see below). They also provide the minimum information on which to base a review of proposed protocols. Important limitations such as the duration of treatment, maximal recommended dose exclusions and special monitoring requirements must be clearly stated in the Usability Guidelines.

The TGA will review the summary information documents prepared for HREC(s). The TGA review will focus on the 'Usage Guidelines' and 'Summary data sheets'. If it is considered appropriate, the TGA will make additional comments to the sponsor's 'Usage Guidelines' under the clearly identified heading 'TGA Comment' (See **Appendix 6, Document 3**).

TGA Review of CTX Applications for Medicines

There are two tiers of evaluation of applications for clinical trials of medicines under the CTX Scheme. These reflect the types of data submitted in support of an application.

A 30 working day period for evaluation of a CTX application applies when the supporting data relates only to chemical, pharmaceutical and biological issues. A 50 working day period applies for applications supported by chemical, pharmaceutical and biological, pharmaco-toxicological and clinical data. These evaluation times commence from the date of acceptance of the application or receipt of the appropriate fee, whichever is the later day.

Sponsors should not assume that the TGA has received an application under the CTX Scheme unless a formal acknowledgment is received from the TGA. If the data supplied with the CTX application does not comply with these guidelines, the application may be returned unevaluated. If no objections are raised by the TGA Delegate before the end of the 30 or 50 working day period, the sponsor will be formally advised in writing and the trial may proceed, subject to HREC approval. The sponsor must ensure that the trial does not commence until written advice has been received from the TGA and HREC approval has been obtained.

If, during the evaluation period, the evaluator considers that the application is in some way deficient, the TGA may ask the sponsor for clarification. If there are significant unresolved issues, further information may be requested from the sponsor. Such a request has the effect of interrupting the 50-day evaluation clock; the sponsor may respond only once, and must do so within 30 working days from the date of the request. If a response is not received within that time the application will lapse.

As a rule, significant amounts of new data should not be provided with the sponsor's response. Following receipt, the TGA will review the response within 20 working days. If the sponsor wishes to provide significant amounts of new data in response to questions, the TGA may seek to negotiate a longer period in which to review the new data.

If the application is acceptable, the sponsor will be advised that there are no objections to the supply of the medicine under the CTX Scheme. If the response is unsatisfactory the sponsor may be advised that the CTX application is rejected. The TGA's decision may be appealed under Section 60 of the *Therapeutic Goods Act 1989*.

Conduct of a trial under the CTX Scheme must also be approved by the responsible HRECs. Applications can be lodged simultaneously with the TGA and the institution(s) at which studies are proposed to be conducted. If the application is lodged simultaneously with the TGA and HREC(s), the sponsor is required to convey any TGA comments or revisions on the application and/or objections to all the HREC(s).

The sponsor must also notify the TGA if an HREC objects to a trial. Any other HRECs that have under consideration, or have approved, a protocol for a substantially similar trial must also be notified by the investigator(s) and/or sponsor if another HREC objects to a trial.

Administrative Requirements for CTX Applications for Medicines

Address for applications

The completed 'Supply of Unapproved Therapeutic Goods under the Clinical Trial Exemption Scheme, Part 1 - The CTX Application' form and a cheque for the evaluation fee should be forwarded to:

By post
The Business Management Unit
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
Australia

By courier
The Business Management Unit
Therapeutic Goods Administration
136 Narrabundah Lane
SYMONSTON ACT 2609
Australia

A copy of the form and accompanying data should be forwarded to:

By post
Experimental Drugs Section
Drug Safety and Evaluation Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
Australia

By courier
Experimental Drugs Section
Drug Safety and Evaluation Branch
Therapeutic Goods Administration
136 Narrabundah Lane
SYMONSTON ACT 2609
Australia

Fees

A fee is payable for evaluation of an application under the CTX Scheme. Processing of an application will not commence until the evaluation fee is paid. The level of fees is set out in Schedule 9 of the Therapeutic Goods Regulations 1990 and a copy of a summary of the current schedule of fees may be obtained from the TGA Information Officer (phone 1800 020 653, fax (02) 6232 8605) or from the TGA's Internet home page at www.tga.gov.au.

Language

All information supporting an application must be in English and must be legible. Where material is not originally in English a full translation must be submitted together with the original documentation.

Size and Binding

All data including supplementary data, submitted in support of an application should be bound. Binders with durable covers containing A4 paper, which can be dismantled and reassembled, are required (it is preferred that the binder is capable of remaining open when lying flat on a desk). External dimensions of the binders should not exceed 290 x 370 mm and 80 mm in thickness.

The scientific summaries in Parts 2, 3 and 4 should not exceed 60 pages in total.

Labelling of Data

All copies of the application should be labelled with the generic (trade or code) name of the medicine, name of sponsor, volume number if appropriate, and the number of the copy.

Cross-Referencing

The CTX application should be presented in a manner sufficient for the TGA to evaluate. Data submitted in other applications must not be referred to unless further copies are included, except when extension of an existing clinical trial program is sought.

Pagination and Indexing

All pages of information supporting an application should be numbered in a logical and easily followed manner. An index based on a coherent system of pagination, and if relevant, volume numbering, should be provided.

Nomenclature

Each active and inactive constituent in the investigational product must be described by:

(a) its Australian approved or monograph name (see the TGA document *Approved Terminology for Drugs*); or
(b) where there is no approved or monograph name, the non-proprietary designation or other descriptive name by which it can be readily identified; or

(c) a laboratory code. The constituent should be described as actual substance included in the formulation, e.g. as a salt not base, hydrate etc, where applicable.

Quantitative Units

Units must always be stated and usually be in System International (SI) form.

Variations to a Clinical Trial Program and/or Product - for Medicines

Extensions to a clinical trial program

The sponsor may request HREC approval for additional trials consistent with the Usage Guidelines without the need to make further applications to the TGA.

A clinical trial program initially approved under the CTX Scheme may be extended beyond the approved Usage Guidelines by:

- a further application under the CTX Scheme or
- notification under the CTN Scheme.

A further application under the CTX Scheme should include:

- revised Usage Guidelines;
- an updated summary of chemical, pharmaceutical and biological documentation or a statement that no changes have been relevant to any aspect of the prior summary;
- an updated summary of pharmaco-toxicological documentation and/or clinical documentation, where relevant;
- updated documentation of fatal or life-threatening adverse events;
- revised HREC documentation, as appropriate;
- or a statement that no changes have been made relevant to any aspect of the previously submitted data, other than that which is the topic of the extension application.

Such applications will be treated as initial applications with a 30 or 50 working day review period, as appropriate for the type of data submitted. Fees are payable accordingly. Changes to previously submitted documents should be highlighted.

All parties involved in the planning, approval and conduct of clinical trials that involve the use of unmarketed products should consider mechanisms for access to continued treatment with those unmarketed products by patients for whom treatment has been found to be effective and where long term therapy would be appropriate following completion of the trial. Parties should therefore consider including a post study supply component in the research protocol.

Variations to pharmaceutical data (Abbreviated application)

Once a medicine is approved for use in a clinical trial under the CTX Scheme, significant changes should not be made to that medicine product while it is being used in clinical trials without the prior approval of the TGA. This includes changes to the method of synthesis of the active raw material, changes to the formulation and method of manufacture of the

finished product, and changes to the specifications of the active raw material and finished product. It also includes changes to the shelf life of the finished product unless the option of continuing stability testing throughout the trial has been chosen.

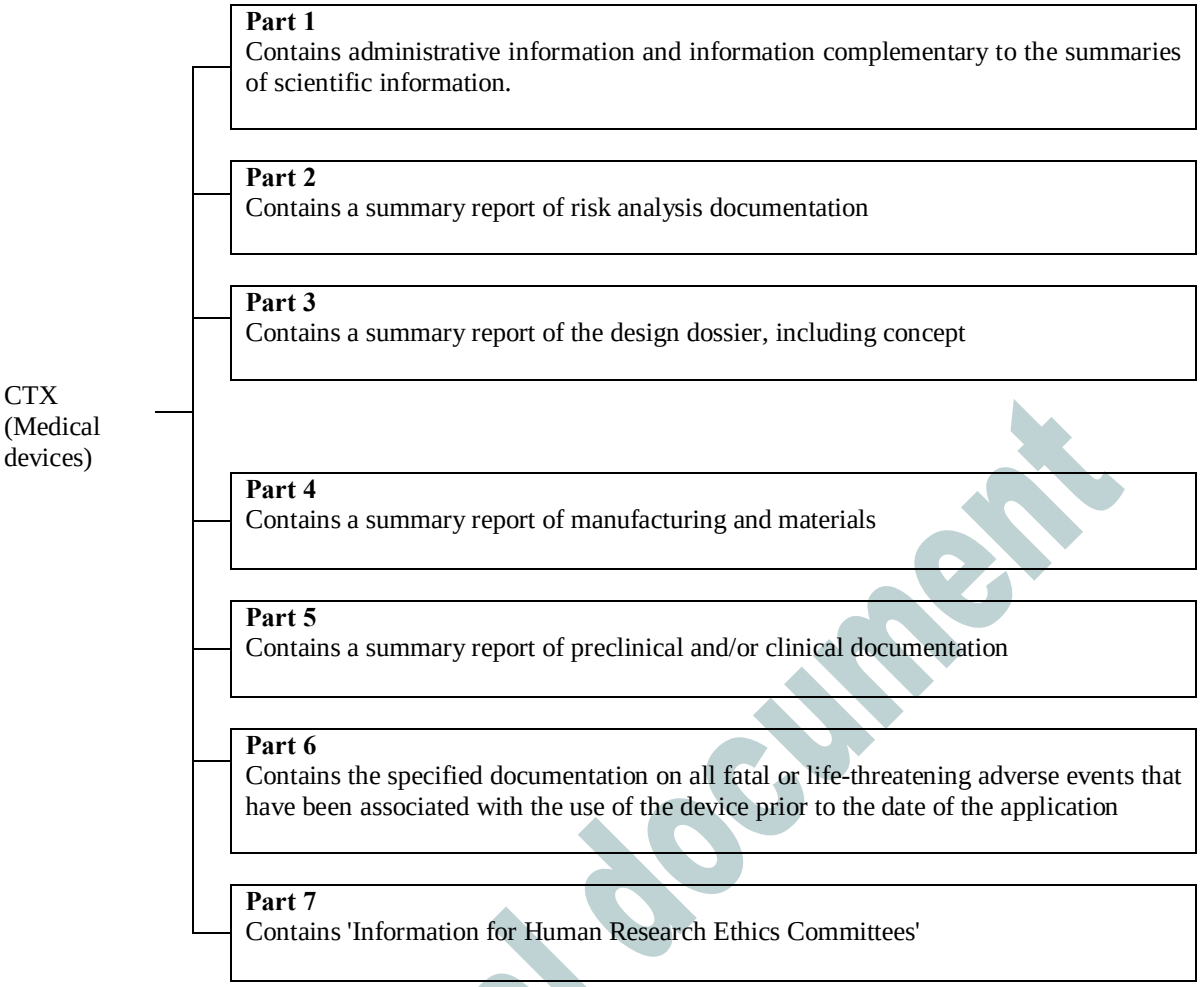
If pharmaceutical changes are proposed, an abbreviated CTX application should be submitted. It will qualify for a 30 working day review period if the application does not need to be supported by further clinical or toxicological data. The application should refer to previous applications in respect of any aspects that are unchanged, eg. Usage Guidelines.

Some exceptions apply to this policy, in line with those that apply to registered medicine products. Appendix 7 of the Australian Guidelines for the Registration of Drugs (AGRD), Vol 1, 2nd Edition, July 1994, defines certain changes which may be made without the prior approval of the TGA. That policy, and the self-assessable changes policy detailed in Appendix 8 of the AGRD, also apply to approved clinical trial products. Notifications of changes to clinical trial products should be made to the Experimental Drugs Unit, Drug Safety and Evaluation Branch, and should be accompanied by a statement that no changes have been made to the product other than those specified in the notification.

CTX Application Format and Content for Clinical Trials of Medical Devices

Submission of clinical data for medical devices under the CTX scheme must comply with *ISO Standard 14155*. (Note: This Standard is being revised in combination with European standard EN540: 1993 and will form a single Standard called *Clinical Investigation of Medical Devices*). Prior discussion with the TGA allows areas of difficulty to be identified at an early stage.

A CTX application for medical devices should be presented in 7 parts. Two copies of the complete application are required to allow simultaneous evaluation in different sections of TGA. The accompanying figure provides a graphic representation of these parts.



A more detailed description of each part is provided below:

- **Part 1** - Administrative information and information complementary to the summaries of scientific information.

  Part 1 provides a very brief overview of information complementary to the summaries of scientific information. It should contain any necessary covering letter or introduction, the application form (CTX Part 1, **Appendix 4**) and information under the heading 'Particulars of the Product and Trial' (**Appendix 5**). The formats shown in the above mentioned appendices should be used and each section should be completed. With respect to the 'Particulars of the Product and Trial', no reference should be made to data held elsewhere. The words ‘Not Applicable’ should be entered where appropriate.

- **Parts 2, 3, 4 and 5** - Summaries of scientific data

  A declaration by a medical or scientific adviser to the sponsor is required, stating that the summaries are an accurate account of the data and that it is reasonable for the study to proceed.

  The summaries will reflect the individual studies carried out by or on behalf of the sponsor, and studies in the published literature. A separate summary of each individual

study may not be necessary if a series of related studies could be summarised together. Interpretative discussion of the scientific significance of the results of each study, or series of related studies, must be included. Tabular presentation is preferred when data from a number of studies are presented in a comparative way.

The degree of flexibility employed in data requirements is governed by the type of product, stage of development and the proposed clinical trials. The technical content of the summaries may be appropriately modified for specific cases, whilst following the general pattern.

General rather than comprehensive guidance is provided below. If the applicant is in doubt as to the data to support a specific application then advice should be sought from the CAB.

- **Part 2** - Summary report of risk analysis documentation

  All applications for a CTX clinical trial must include a summary of the risk analysis for the device. As a guide to what is required, sponsors are referred to standard EN1441, a European standard relating to risk analysis and medical devices.

  This standard specifies a procedure to investigate, using available information, the safety of a medical device, by identifying hazards and estimating the risks associated with the device. This standard does not stipulate levels of acceptability which, because they are determined by a multiplicity of factors, cannot be set down in a standard.

  Sponsors will need to clearly state and justify all assumptions, the derivation of all data, the use of particular analysis techniques and consequential decisions.

- **Part 3 -** Summary of the design dossier, including concept and intended performance.

  This report should include the results of all available studies in relation to:

  - biomaterials and biocompatability;
  - method of sterilisation and validation; and
  - preclinical animal data

  Tabular format/listings should be used whenever possible to enhance the clarity of presentation.

- **Part 4** - Manufacture and materials

  Medical devices that are in the final form, suitable for release onto the market, are expected to be supported by evidence of quality management system certification. Initial evidence of manufacturing may consist of documented elements of a quality management system (eg a Plant Master File for the manufacturing site). Medical devices, still in development stages, do not require quality management system certification to be used in a clinical trial.

Evidence of pre clinical testing of new materials for biocompatibility, toxicity and mutagenicity must be included in the summary of materials. Where appropriate, this may include the results of animal studies.

- **Part 5** - Preclinical and/or Clinical Documentation

  Summaries of reports and evaluations of any preclinical and/or clinical studies carried out with each product or its constituents, which in the view of the sponsor are relevant to the assessment of safety, quality or efficacy of the device should be provided in this Part. References to relevant publications or other studies should be included if relevant to the safety evaluation.

  There is no formal requirement for prior studies in humans. However, if any studies have been undertaken and they have any relevance to the device's safety, they must be reported in the summary. Detailed documentation of fatal or life-threatening adverse events should also be provided separately in Part 6 of the application.

- **Part 6** - Documentation of fatal or life-threatening adverse events

  Documentation of all reported fatal or life-threatening adverse events associated with the use of the device prior to the date of the application must be included in this section. Relevant reports should be included from all countries in which the drug has been used. The Council for International Organisations of Medical Sciences (CIOMS) format is satisfactory for reports not originating in Australia.

  'Life-threatening' in this context means that 'the patient was, in the view of the investigator, at immediate risk of death from the event as it occurred' (ie. it does not include an event that, had it occurred in a more serious form, might have caused death).

  'Associated with the use of the device' means that there is a reasonable possibility that the event may have been caused by the device.

  This documentation is in addition to the description of adverse events included in the summary of 'Clinical Documentation' where other adverse events will be identified and discussed.

  For details of reporting requirements for adverse events that occur during the period in which a trial is conducted under the CTX Scheme, for both adverse events in overseas countries and in Australia, refer to 77 of this document.

- **Part 7** - Summary Information for Human Research Ethics Committees

  In order to assist the responsible HREC(s), sponsors of investigational medical devices should prepare a separate section of summary information for HRECs. Information should include (but should not be limited to):

  - a summary statement (**Appendix 6, Document 1**);

  - the status of the medical device in overseas countries with similar regulatory procedures (**Appendix 6, Document 2**);

- a summary data sheet on risk analysis documentation;
- a summary data sheet on design dossier, including concept;
- a summary data sheet on manufacturing and materials;
- a summary data sheet on preclinical and/or clinical documentation;
- usage guidelines for the device under investigation (**Appendix 6, Document 4**).

Summary data sheets should be prepared by the sponsor to summarise for HRECs the relevant scientific data to support the proposed trial. Separate headings should be used for each type of data.

A recent (less than six months old) edition of the Investigator's Brochure (ISO/CD 14155-1 para 3.13) may be submitted in place of the summary statement and summary data sheets. If this option is taken, it is important to append a safety update if there have been any significant events since the Investigator's Brochure was prepared.

The status of the medical device in overseas countries can include both marketing and clinical trial status.

The Usage Guidelines are a key document in the CTX application. These describe the boundaries of the approved study, such that further trials that are consistent with the Usage Guidelines can be conducted without further TGA approval (except for significant changes to design or materials of the device). They also provide the minimum information on which to base a review of proposed protocols. Important limitations such as patient selection criteria for the device, special monitoring requirements and procedures for long term follow up of trial subjects must be clearly stated in the Usage Guidelines.

The TGA will review the summary information documents prepared for HREC(s). The TGA review will focus on the 'Usage Guidelines' and 'Summary data sheets'. If it is considered appropriate, the TGA will make additional comments to the sponsor's 'Usage Guidelines' under the clearly identified heading 'TGA Comment'.

TGA Review of CTX Applications for Medical Devices

A 50 working day period applies for CTX applications for medical devices. The evaluation time commences from the date of acceptance of the application or receipt of the appropriate fee; whichever is the later day.

Sponsors should not assume that the TGA has received an application under the CTX Scheme unless a formal acknowledgment is received from the TGA. If the data supplied with the CTX application does not comply with these guidelines, the application may be returned unevaluated. If no objections are raised by the TGA Delegate before the end of the 50 working day period, the sponsor will be formally advised in writing and the trial may proceed, subject to HREC approval. The sponsor must ensure that the trial does not

commence until written advice has been received from the TGA and HREC approval has been obtained.

If, during the evaluation period, the evaluator considers that the application is in some way deficient, the TGA may ask the sponsor for clarification. If there are significant unresolved issues, further information may be requested from the sponsor. Such a request has the effect of interrupting the 50-day evaluation clock; the sponsor may respond only once, and must do so within 30 working days from the date of the request. If a response is not received within that time the application will lapse.

As a rule, significant amounts of new data should not be provided with the sponsor's response. Following receipt, the TGA will review the response within 20 working days. If the sponsor wishes to provide significant amounts of new data in response to questions, the TGA may seek to negotiate a longer period in which to review the new data.

If the application is acceptable, the sponsor will be advised that there are no objections to the supply of the medicine under the CTX Scheme. If the response is unsatisfactory the sponsor may be advised that the CTX application is rejected. The TGA's decision may be appealed under Section 60 of the *Therapeutic Goods Act 1989*.

Conduct of a trial under the CTX Scheme must also be approved by the responsible HRECs. Applications can be lodged simultaneously with the TGA and the institution(s) at which studies are proposed to be conducted. If the application is lodged simultaneously with the TGA and HREC(s), the sponsor is required to convey any TGA comments or revisions on the application and/or objections to all the HREC(s).

The TGA must also be notified by the sponsor if an HREC objects to a trial. Any other HRECs that have under consideration, or have approved, a protocol for a substantially similar trial must also be notified by the investigator(s) and/or sponsor if another HREC objects to a trial.

Administrative Requirements for CTX Applications for Medical Devices

Address for applications

The completed 'Supply of Unapproved Therapeutic Goods under the Clinical Trial Exemption Scheme, Part 1 - The CTX Application' form and a cheque for the evaluation fee should be forwarded to:

By post
The Business Management Unit
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
Australia

By courier
The Business Management Unit
Therapeutic Goods Administration
136 Narrabundah Lane
SYMONSTON ACT 2609
Australia

A copy of the form and accompanying data should be forwarded to:

By post
Clinical Section
Office of Devices, Blood and Tissues
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
Australia

By courier
Clinical Section
Office of Devices, Blood and Tissues
Therapeutic Goods Administration
136 Narrabundah Lane
SYMONSTON ACT 2609
Australia

Fees

A fee is payable for evaluation of an application under the CTX Scheme. Processing of an application will not commence until the evaluation fee is paid. The level of fees is set out in Schedule 5 of the Therapeutic Goods (Medical Devices) Regulations 2002 and a copy of a summary of the current schedule of fees may be obtained from the TGA Information Officer (phone 1800 020 653, fax (02) 6232 8605) or from the TGA's Internet home page at www.tga.gov.au.

Language, pagination and indexing

Submissions must be in English, typed on A4 paper in type size no smaller than 10 point, and presented in labelled and numbered volumes. The submission should include a Table of Contents and follow the methodology prescribed in European Standard EN540: 1993.

Notification of Trials Conducted under a CTX Approval - Medicines and Medical Devices

Sponsors of clinical trials conducted under a CTX application must notify the TGA within 28 days of the commencement of supply of the goods at each site using the CTX Part 2 form **(Appendix 4)**. The notification, containing certifications of the sponsor, principal investigator, HREC and Approving Authority, is required to inform the TGA of the conduct of each specific trial. The notification is intended to demonstrate that all of the parties involved in the conduct of individual trials have complied with legislative and regulatory requirements and agree to release information to the TGA about the conduct of the trial in the event of an inquiry or audit of the trial of the TGA. There is no fee for notification of trials under the CTX scheme.

Information Required on Completion of CTX Trials for Medicines and Medical Devices

The TGA maintains a record of each CTX trial and each trial centre conducting a trial under the CTX application. To maintain the record for each trial, the TGA must be notified of the following information:

- the date the trial was completed (ie last date of completion for all sites. It is not necessary to notify completion dates for individual sites);
- the reason the trial ceased (eg concluded normally; insufficient recruits etc); and
- any changes to the trial in respect of information previously submitted to TGA.

The information contained under the first two dot points above can be notified to the TGA using a *Clinical Trial Completion Advice - CTN and CTX Schemes* form. A copy of this form can be found in **Appendix 3**.

REPORTING OF ADVERSE REACTIONS ARISING DURING CLINICAL TRIALS OF MEDICINES

Definitions

The ICH definitions of adverse events, adverse reactions, serious adverse reactions and unexpected reactions apply within Australia:

Adverse Events (or Adverse Experiences)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse drug reaction (ADR)

For unapproved medicines: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding *marketed medicinal products*: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or Product Information/package insert/summary of product characteristics for an approved product).

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect.

Note: the term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Reporting of adverse events and reactions occurring in clinical trials

Australia has adopted two CPMP/ICH documents relating to the reporting of adverse events and reactions arising during the clinical development of medicines. The first of these is the '*Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95)', an internationally accepted standard for designing, conducting, recording and reporting of clinical trials. In addition, the TGA has adopted the *'Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)'* in principle, particularly its definitions and reporting time frames. This latter document is an internationally accepted standard for the reporting of important safety information arising during the clinical development of medicines. The definitions and standards for expedited reporting have application in Australia in relation to clinical trials, the Special Access Scheme, the Authorised Prescriber mechanism and use of unapproved products through personal importation.

Section 5.17 of the *Note for Guidance on Good Clinical Practice* makes the following comments in relation to Adverse Drug Reaction Reporting:

> "The sponsor should expedite the reporting to all concerned investigator(s)/institution(s), to the IRB(s)/IEC(s), **where required**, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.
>
> Such expedited reports should **comply with the applicable regulatory requirement(s)** and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.
>
> The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, **as required by applicable regulatory requirement(s)**."

The above passages have been highlighted to indicate that the CPMP/ICH guidelines are not absolute and may, in fact, be overridden by the requirements of individual regulatory agencies as appropriate, to address matters relevant to local conditions or culture.

Thus, whilst the TGA has adopted these CPMP/ICH documents and the definitions and reporting time frames therein, there are important TGA requirements with which sponsors must comply. Sponsors should read the information set out below carefully, particularly with regard to reporting requirements and format. Annotated copies of theses CPMP/ICH Notes for Guidance, containing comments outlining Australian requirements, are available from the TGA website:

> http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm

The table below summarises reporting requirements for sponsors of clinical trials and clinical investigators.

Reporter →	Reports what?	→ To whom?	→In what format?	→ In what timeframe?
Sponsor of trial	Serious and unexpected adverse drug reactions	TGA*	ADRAC blue card[$]	For fatal or life-threatening ADRs, send initial report within 7 calendar days of first knowledge. Follow up with complete report within 8 additional calendar days. For all other serious and unexpected ADRs, full report no later than 15 calendar days of first knowledge by the sponsor.
	Other reactions and adverse events	TGA	Tabulation	On request by TGA.
Clinical investigator(s)	Adverse reactions/events	HREC	As required by HREC	As required by HREC
		Sponsor of trial	As per study protocol	As per study protocol

* Report should be clearly marked 'Clinical trial ADR' and sent to:

The Medical Adviser
Experimental Drugs Section
Drug Safety and Evaluation Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

$ Or an appropriate format that contains the same information

The principles for reporting adverse reactions occurring during a clinical trial of a medicine are the same whether the trial is being conducted under the CTX or CTN Scheme:

- The clinical investigator has a responsibility to ensure the conduct of the trial, including the monitoring of safety and reporting of adverse outcomes, complies with the study protocol. The investigator should report immediately to the sponsor and HREC any serious adverse outcomes unless they are identified in the protocol or HREC documents as not requiring immediate reporting. Initial reports should be followed by detailed written reports including comment on potential confounding factors, results of investigations, treatment required and outcome. The sponsor and the principal investigator should review the adverse outcome in the context of known information on the medicine and make a determination as to whether the event was drug-related (ie an adverse reaction).

- Sponsors of clinical trials are required to report to TGA **single cases of serious and unexpected adverse reactions**. Fatal or life-threatening ADRs should be reported within **seven calendar days** of the reaction first being notified to the sponsor. This should be followed by as complete a report as possible within **eight additional calendar days**. All other serious and unexpected ADRs should be reported to TGA within 15 calendar days of first knowledge of the sponsor.

- Information should be provided in the form of a detailed summary (ie. the ADRAC 'Blue Card' format, see **Appendix 7**). Even if initial information is scanty, these details should be forwarded to the TGA pending receipt and provision of further data. This procedure should be followed even when the medicine in question is the subject of an application for registration and under evaluation by the TGA.

- Sponsors of clinical trials are also required to communicate rapidly to the TGA information that has an important bearing on the benefit-risk assessment of the investigational product or that would be sufficient to consider changes to the overall conduct of the clinical trial. Such information may arise as a result of the sponsor's monitoring of the trial, including an internal statistical analysis of data. This issue is addressed under Item 3.A.2 '**Other observations**' of the *Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)*; and

- Sponsors are **not required, as a matter of routine, to submit individual patient reports** to the TGA of suspected adverse drug reactions occurring with use of the same product in **another country**, even if a trial is ongoing at Australian sites. However, the TGA requires that sponsors advise the Experimental Drugs Section of the Drug Safety and Evaluation Branch **within 72 hours** of **any significant safety issue** which has arisen from an analysis of overseas reports **or action with respect to safety which has been taken by another country's regulatory agency**. This advice must include the basis for such action.

  Sponsors should also inform any Australian investigator(s) and, through the investigator, the HREC(s) of this information. Such information may be new and have an impact on the continued ethical acceptability of the trial, or may indicate the need for amendments to the trial protocol, including monitoring of safety. The TGA also requires that sponsors be able to provide promptly clinical details of any individual overseas adverse drug reaction reports **if requested**.

Because the CTN Scheme is a notification scheme, it is possible that the TGA will not have reviewed any safety (or other) data concerning the trial when an adverse reaction is reported. Therefore, reports of adverse reactions arising from a CTN trial medicine could have little value if not accompanied by appropriate information or interpretation. Appropriate supporting information could include a copy of the most recent Investigator's Brochure and/or the trial protocol.

The following **TGA advice** is intended to provide additional guidance to sponsors of clinical trials:

· *Managing blinded therapy cases - breaking the trial code*

This issue is covered under item 2.D of the ICH *Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*. In general, when a serious reaction is considered reportable on an 'immediate' basis (ie drug related and unexpected), it is recommended that the trial code be broken by the sponsor, but only for that particular patient, even if the investigator has not unblinded the case. This may necessitate withdrawal of the subject from the trial.

Retention of the blind or code for the patient is understandable when the fatal or serious outcome is identical to or closely resembles the primary efficacy endpoint of the study. These outcomes would be considered to be 'disease-related' and exempted from expedited reporting. However, where it becomes apparent from the sponsor's own monitoring and analysis of data that the number of cases of a fatal or serious nature is in excess of that which could reasonably be expected, sponsors should reconsider the issue of blinding and report this information to the TGA. **The trial protocol should state explicitly how these issues are to be handled.**

Breaking a trial code may also be required in the interests of public safety. However this is a serious undertaking which has the capacity to invalidate the entire clinical trial. Sponsors and ethics committee members are invited to consult with the TGA should such a situation arise.

· *Reporting of overdoses*

Sponsors should report serious and unexpected adverse reactions that occur as a result of cases of accidental or intentional overdose. This includes reports that indicate that the taking of the suspect drug led to suicidal ideation and a subsequent overdose of the suspected medicine or other medication. Reports of overdose with no associated adverse reactions should not be reported in an expedited fashion.

· *Reporting of non-serious and expected adverse drug reactions and adverse events*

Non-serious and expected adverse reactions and adverse events should be recorded as part of Good Clinical Practice (GCP). It is imperative that the sponsor, in accordance with GCP principles, perform an internal statistical analysis of these data, and advise the TGA of any safety issues which emerge during this process. Such data do not need to be submitted on a routine basis to the TGA during the trial, but should be available for submission to the TGA **on request**, and where applicable, submitted as part of an application for registration.

Sponsors are expected to maintain up to date tabulations and/or line listings of all adverse reactions.

When data on non-serious events or expected adverse reactions are requested by the TGA, initial presentation will be accepted in a tabular format, with further clinical details available at the request of the TGA. The minimal reporting details should include:

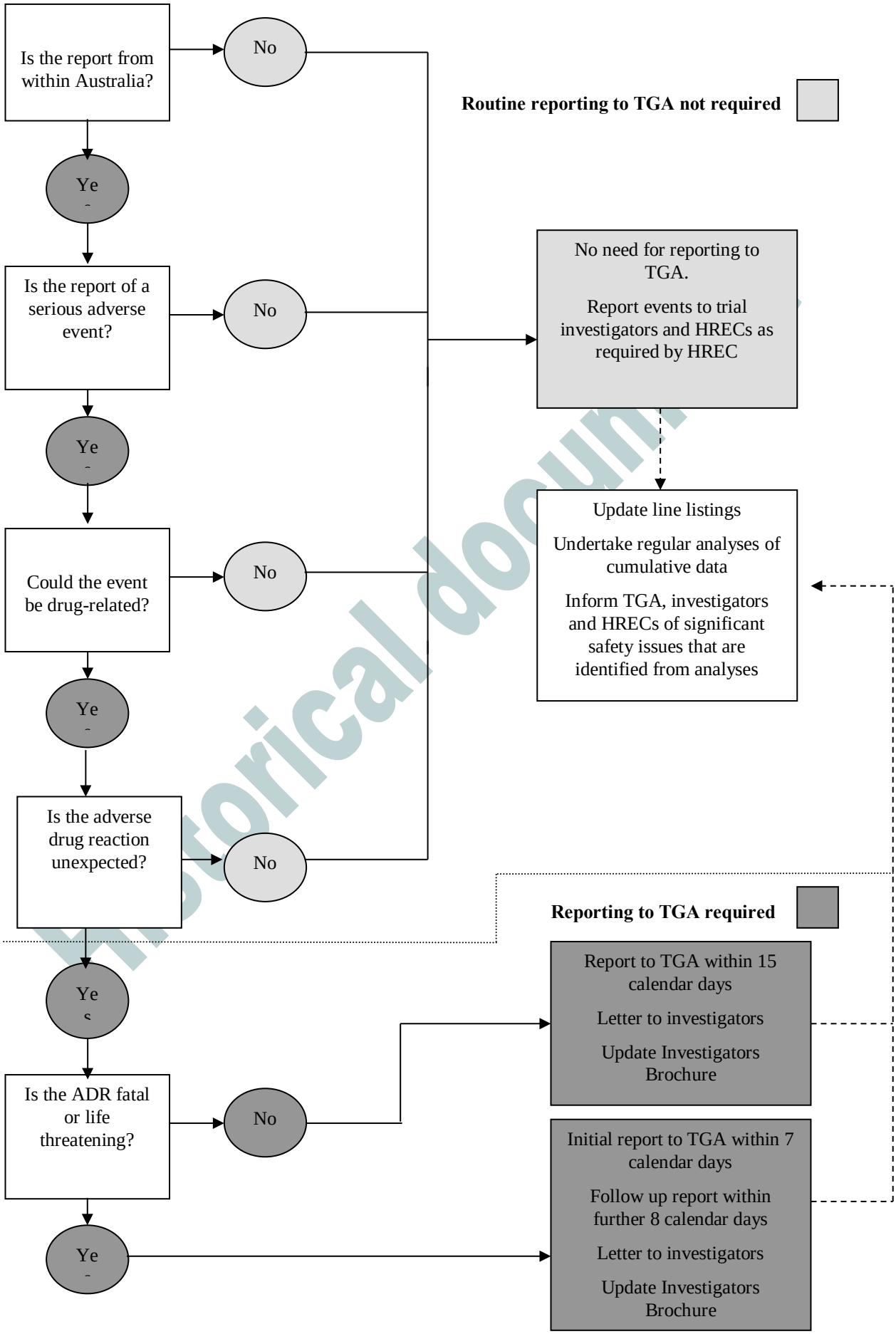
- subject identification codes
- age

- sex
- name(s) of the medicine(s) involved
- dose and duration of treatment
- nature of the reaction
- condition being treated
- potentially confounding factors
- outcome

· Adverse reactions which currently appear in the Australian Product Information and/or Investigator's Brochure but are described as having no established causal relationship should be considered unexpected for the purposes of reporting to the TGA. If a previously unexpected adverse reaction is added to the Australian Investigator's Brochure, then that particular reaction ceases to be unexpected in Australia.

· The following adverse event reporting algorithm is intended to assist sponsors determine which events are to be reported to TGA:

Clinical Trial Event Reporting Algorithm for Sponsors



REPORTING OF ADVERSE OUTCOMES DURING CLINICAL TRIALS OF MEDICAL DEVICES

Definitions

The definitions applied for the purposes of reporting adverse incidents for medical devices are those defined in *ISO/CD 14155-2.2 January 2000*:

Adverse Event: Any undesirable clinical occurrence in a subject whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device.

Adverse Device Event: A clinical sign, symptom or condition that is causally related to the device implantation procedure, the presence of the device, or the performance of the device system.

Serious Adverse Event: Any adverse medical occurrence that

1. Led to a death
2. Led to a serious deterioration in health of a patient user or other. This would include:
   a. a life threatening illness or injury
   b. a permanent impairment of body function or permanent damage to a body structure
   c. a condition requiring hospitalisation or increased length of existing hospitalisation
   d. a condition requiring unnecessary medical or surgical intervention
   e. foetal distress, foetal death or a congenital abnormality/ birth defect
3. Might have led to death or a serious deterioration in health had suitable action or intervention not taken place. This includes:
   a. a malfunction of a device such that it has to be modified or temporarily/permanently taken out of service
   b. a factor (a deterioration in characteristics or performance) found on examination of the device.

Serious Adverse Device Event: A device related serious adverse event

Unanticipated Device Related Adverse Event: Any undesirable clinical occurrence in a subject considered to be device related and not listed in the device technical manuals (or not listed in the appropriate section on the Adverse Event case report form).

Reporting requirements for clinical trials conducted under the CTN and CTX Schemes

Reporter	→ Reports what?	→ To whom?	→ In what format?	→ In what timeframe?
Sponsor of trial	Serious and unexpected adverse device events	TGA*	Medical Device Incident Report form[$]	For fatal or life-threatening events, send initial report within 7 calendar days of first knowledge. Follow up with complete report within 8 additional calendar days. For all other serious unanticipated device related events, full report no later than 15 calendar days of first knowledge by the sponsor
	Other adverse device events and adverse events	TGA	Tabulation	On request by TGA.
Clinical investigator(s)	Adverse device events and adverse events	HREC	As required by HREC	As required by HREC
		Sponsor of trial	As per study protocol	As per study protocol

* Report should be clearly marked 'Clinical trial Adverse Device Event' and sent to:

The Medical Officer
Office of Devices, Blood and Tissues
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

$ Or an appropriate format that contains the same information

The principles for reporting adverse events occurring during a clinical trial of a medical device are the same whether the trial is being conducted under the CTX or CTN Scheme:

- The clinical investigator has a responsibility to ensure the conduct of the trial, including the monitoring of safety and reporting of adverse outcomes, complies with the study protocol. The investigator should report immediately to the sponsor and HREC any serious adverse outcomes unless they are identified in the protocol or HREC documents as not requiring immediate reporting. Initial reports should be followed by detailed written reports including comment on potential confounding factors, results of investigations, treatment required and outcome. The sponsor and the principal investigator should review the adverse outcome in the context of information known about the medical device and make a determination as to whether the event was device related.

- Sponsors of clinical trials are required to report to TGA **single cases of serious unanticipated device related adverse events**. Of these, fatal or life-threatening events should be reported within seven calendar days of the reaction first being notified to the sponsor. This should be followed by as complete a report as possible within eight additional calendar days. All other serious unanticipated device related adverse events should be reported to TGA within 15 calendar days of the sponsor. Information should be provided in the form of the Medical Device Incident Report (**Appendix 8**). Even if initial information is scanty, these details should be forwarded to the TGA pending receipt and provision of further data. This procedure should be followed even when the device in question is the subject of an application for registration/listing and under evaluation by the TGA.

- Sponsors of clinical trials are also required to communicate rapidly to the TGA information that has an important bearing on the benefit-risk assessment of the investigational product or that would be sufficient to consider changes to the overall conduct of the clinical trial. Such information may arise as a result of the sponsor's monitoring of the trial, including an internal statistical analysis of data.

- Sponsors are **not required, as a matter of routine, to submit individual patient reports** to the TGA of suspected adverse device related events occurring with use of the same product in **another country**, even if a trial is ongoing at Australian sites. However, the TGA requires that sponsors advise the Chief Clinical Adviser of the Office of Devices, Blood and Tissues **within 72 hours** of **any significant safety issue** which has karisen from an analysis of overseas reports **or action which has been taken by another country's regulatory agency**. This advice must include the basis for such action.

  Sponsors should also inform any Australian investigator(s) and, through the investigator, the HREC(s) of this information. Such information may be new and have an impact on the continued ethical acceptability of the trial, or may indicate the need for amendments to the trial protocol, including monitoring of safety. The TGA also requires that sponsors be able to provide promptly clinical details of any individual overseas **if requested**.

Because the CTN Scheme is a notification scheme, it is possible that the TGA will not have reviewed any safety (or other) data concerning the trial when an adverse event is reported. Therefore, reports arising from a CTN trial could have little value if not accompanied by appropriate information or interpretation. Appropriate supporting information could include a copy of the most recent Investigator's Brochure and/or the trial protocol.

- *Reporting of non-serious and anticipated device related adverse events and adverse events*

  Non-serious and anticipated device related adverse events and adverse events should be recorded as part of Good Clinical Practice (GCP). It is imperative that the sponsor, in accordance with GCP principles, perform an internal statistical analysis of these data, and advise the TGA of any safety issues which emerge during this process. Such data do not need to be submitted on a routine basis to the TGA during the trial, but should be available for submission to the TGA **on request**, and where applicable, submitted as part of an application for registration.

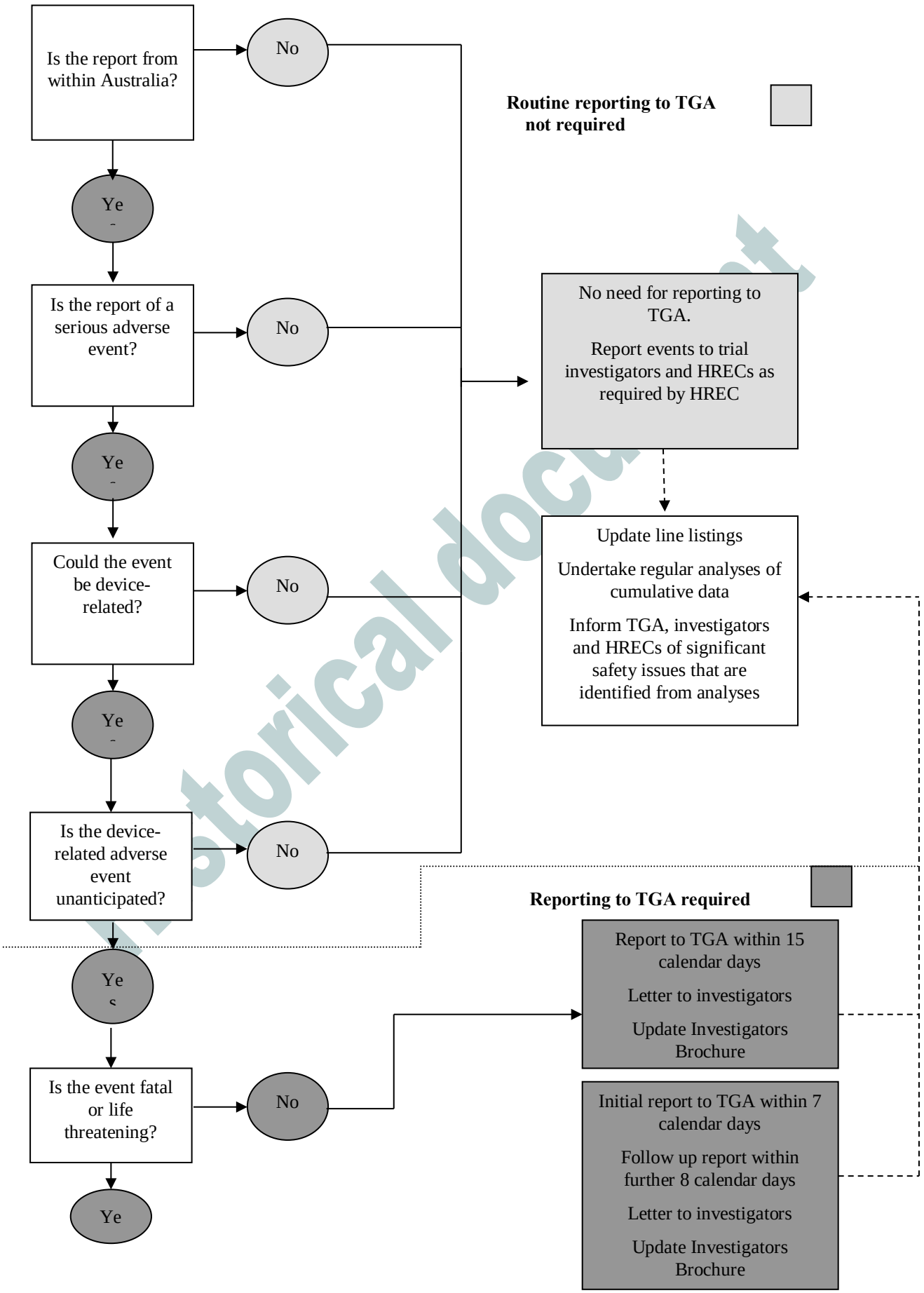
Sponsors are expected to maintain up to date tabulations and/or line listings of all adverse device events.

When data on non-serious events or anticipated device related adverse events are requested by the TGA, initial presentation will be accepted in a tabular format, with further clinical details available at the request of the TGA. The minimal reporting details should include:

- subject identification codes
- age
- sex
- name(s) of the device involved
- nature of the event
- condition being treated
- potential confounding factors
- outcome

· The following adverse event reporting algorithm is intended to assist sponsors determine which events are to be reported to TGA:

Clinical Trial Event Reporting Algorithm for Sponsors



APPENDIX 1
GLOSSARY

Adverse Events (or Adverse Experiences, AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse drug reaction (ADR)

For unapproved medicines: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

> **An Unexpected Adverse Drug Reaction** is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or Product Information/package insert/summary of product characteristics for an approved product).
>
> **A Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) is**:
>
> Any untoward medical occurrence that at any dose:
>
> - Results in death,
> - Is life-threatening,
> - Requires inpatient hospitalisation or prolongation of existing hospitalisation,
> - Results in persistent or significant disability/incapacity, or
> - Is a congenital anomaly/birth defect.

For medical device events: the definitions are contained within the text of this publication.

Appellant

A person seeking a review of a decision under Section 60 of the Act or Regulation 48 of the Medicines Regulations and Regulation 10.7 of the Medical Devices Regulations.

Application

In relation to unapproved therapeutic goods, an application made to the TGA under section 19 or Sections 41HB of the Act (special and experimental uses).

Approving Authority

The body, organisation or institution that approves the conduct of a clinical trial at a particular trial site.

Australian Register of Therapeutic Goods (ARTG)

The ARTG is a computer database established under the *Therapeutic Goods Act 1989* in which most therapeutic goods are required to be entered prior to their supply in, or export from, Australia. *Note:* Some goods are exempted from the requirement to be included in the ARTG, such as products approved for use in clinical trials and the Special Access Scheme.

Bioavailability

The rate and extent of absorption of an active ingredient from a dosage form as determined by its concentration/time curve in the systemic circulation or by its excretion in urine.

Bioequivalence

Two medicinal products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities after administration are similar to such a degree that their effects, with respect to both efficacy and safety will be essentially the same.

Biological products

Products in which the active ingredient is a biological substance including antisera, antivenins, monoclonal antibodies and products of recombinant technology.

Clinical Trial (study)

A planned study in humans designed to investigate and report upon the effectiveness and/or safety of a therapeutic good. In the context of these guidelines, this means a systematic study of a medicine or a medical device, conducted in humans in order to discover or verify the effects of and/or identify the adverse reactions to those products and/or study their absorption, distribution, metabolism and excretion in order to ascertain the efficacy and safety of the products. Each trial is supported by a single protocol, but that protocol may allow the trial to be carried out at a single site or multiple sites.

Clinical Trial Phases

Clinical trials are generally classified according to the phase of development of a medicine. A description of these phases is provided in the text of this publication under the heading 'Classification of Clinical Trials'.

Codes of Good Manufacturing Practice

Principles and practices to be followed in the manufacture of medicines and 'other therapeutic goods' to provide assurance of product quality and compliance with product ARTG registration or listing.

Composite trial site

A grouping of two or more sites participating in a trial, which have a common ethics committee and a common approving authority.

Delegate

An officer who has been given authority by the Minister or Secretary to exercise a power, which the Act or Regulations confer on the Minister/Secretary.

Ethics Committee see 'Human Research Ethics Committee', below

Exempt Goods

Relates to the provisions of Chapters 3 or 4 of the Act, and covers goods that are exempted from the requirement to be included in the Register of Therapeutic Goods or are exempted from licensing requirements.

Formulation

A list of the ingredients used in the manufacture of a dosage form and a statement of the quantity of each ingredient in a defined weight, volume, unit or batch.

Gene and Related Therapies Research Advisory Panel (GTRAP)

A subcommittee of the NHMRC's Research Committee, established in 1994 to provide HRECs with advice about medical, scientific, ethical and safety issues related to gene therapy protocols. It provides advice to researchers to facilitate design of protocols for gene therapy and maintains a register of human gene therapy trials undertaken in Australia. Membership of GTRAP includes gene therapy, xenotransplantation and human stem cell research experts, members of the Gene Therapy Technical Advisory Committee (GTTAC), a representative from the TGA, an ethicist and a lawyer.

Gene Therapy and Related Therapies

As originally conceived, gene therapy is the introduction of DNA (deoxyribonucleic acid) or RNA (ribonucleic acid) into the cells of humans using a gene carrier or 'vector' to carry a gene into cells with a view to integration of the gene into chromosomal DNA and its long

term expression. The NHMRC considers introduction of DNA or RNA into somatic (nonreproductive) cells to be ethically acceptable. However, it considers the introduction of DNA or RNA into germ (reproductive) cells to be ethically unacceptable since there is insufficient knowledge about the possible consequences including hazards and effects on future generations. HRECs would not be expected to receive, and should not approve, research proposals for germ cell gene therapy.

Recent novel and varied methodologies for introducing and modifying gene expression overlap with the traditional concept of gene therapy. These include modifications to immunisation strategies, in which DNA, rather than protein is used to generate an immune response to treat or prevent a chronic viral infection, such as HIV, or as part of cancer treatment. These are considered to be 'related' therapies. If there is any doubt as to whether a research proposal falls within the related therapies, researchers should seek the advice of GTRAP.

Gene Technology Technical Advisory Committee (GTTAC)

A committee established by the *Gene Therapy Act 2000* to provide scientific and technical advice to the Gene Technology Regulator on matters relating to gene technology, genetically modified organisms, genetically modified products and biosafety aspects of gene technology. The expertise of the membership of the committee is wide ranging including, amongst others: molecular biology; plant, microbial, animal or human genetics; virology; biosafety engineering; public health; risk assessment; clinical medicine and microbiology.

Good Clinical Practice

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Human Research Ethics Committee (HREC)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

In the context of this document, an ethics committee, as defined in the *Therapeutic Goods Act* and Regulations, means a committee constituted and operating in accordance with the National Health and Medical Research Council's *Statement on Ethical Conduct in Research Involving Humans*, 1999, and which has notified its existence to the Australian Health Ethics Committee established under the National Health and Medical Research Council Act 1992.

Impurities

Unintended components of the medicine substance or finished product. They may arise from decomposition of the medicine, they may be by-products of the synthesis, solvent or reagent residues, or they may be contamination from other sources.

Informed consent

Consent freely given by a person on the basis of information concerning the potential risks and benefits of the treatment that was sufficient information to allow the person to make an informed decision whether to consent to the treatment or participate in the trial.

Institutional Biosafety Committees (IBCs)

GMAC requires that every organisation intending to carry out work with genetically manipulated organisms (GMOs) that falls within the scope of the GMAC Guidelines establish an Institutional Biosafety Committee to oversee and monitor work at the local level. IBCs undertake the initial assessment of all proposals involving GMOs and suggest revisions before submitting proposals to GMAC.

International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use) (ICH)

A project involving regulatory authorities and pharmaceutical industry experts from Europe, Japan and the United States in discussion of scientific and technical aspects of product registration, resulting in recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration, with a view to reducing the need for duplication of testing and trialling of new medicines.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial may be referred to as the coordinating investigator.

Investigational product

Any investigational medicine or device, reference product or device or placebo being tested or used as reference in a clinical study.

Investigator's brochure

A summary of data consisting of all the relevant information known prior to the onset of a clinical study including, for a medicine, chemical and pharmaceutical data, toxicological, pharmacokinetic and pharmacodynamic data in animals and the results of earlier clinical studies. The results of prior clinical studies in humans (safety and efficacy) should be presented and a discussion of the possible risks and side effects. The information should be updated during the course of the study, if new data arise.

Medicine

A therapeutic good (substance or preparation) that is represented to achieve (or is likely to achieve) its principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body. It may be intended for administration to humans in order to:

- prevent, diagnose, alleviate or cure a disease, ailment, defect or injury; or
- test the susceptibility of a person to a disease or ailment; or
- influence, inhibit or modify a physiological process; or
- influence, control or prevent conception.

Medical Device

Any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process;
- control of conception;

and that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its function by such means; or

an accessory to such an instrument, apparatus, appliance, material or other article.

Multicentre study

A study conducted simultaneously by several investigators at different centres, with identical methods (ie, following the same protocol).

Notification

Advice to the TGA in accordance with the legislation. For unapproved medicines, notifications are required in relation to Regulation 12A (Category A patients under the Special Access Scheme) and Schedule 5A Item 3 (CTN Scheme). For medical devices,

notifications are required in relation to medical device Regulation 7.2 and 8.2 (Category A patients under the Special Access Scheme) and Schedule 4 item 2.3 (CTN Scheme).

In the context of the CTN Scheme, a clinical trial is deemed to have been notified as soon as the requirements set out under Item 3 of Schedule 5A of the Regulations or item 2.3 of Schedule 4 of the medical devices Regulations have been met (ie completion of the CTN form and forwarding it and the relevant fee to the TGA). Once this occurs the exemption under Section 18(1) or Section 41HA comes into effect and the sponsor can supply the goods. Waiting for an acknowledgment from the TGA is not one of the requirements. Thus, a sponsor does not have to wait for the TGA's acknowledgment letter before commencing the trial. (However, it may be advisable for sponsors to wait for the TGA's acknowledgment in case there is anything [such as incomplete information on the CTN form] that might invalidate the notification.)

Office of the Gene Technology Regulator (OGTR)

The Office of the Gene Technology Regulator has been established within the Commonwealth Department of Health and Ageing to provide administrative support to the Gene Technology Regulator in the performance of her functions under the *Gene Technology Act 2000*. The *Gene Technology Act 2000*, which came into force on 21 June 2001, introduces a national scheme for the regulation of genetically modified organisms in Australia, in order to protect the health and safety of Australians and the Australian environment by identifying risks posed by or as a result of gene technology, and to manage those risks by regulating certain dealings with genetically modified organisms.

It oversees the development and use of novel genetic manipulation techniques and has a role to play in the assessment of gene therapy trials if the treatment involves the use of an agent such as genetically modified live organisms (eg a virus) which could potentially harm the community and/or environment.

'Other therapeutic goods'

These are goods previously regulated as therapeutic devices but which no longer satisfy the revised definition of a medical device. These products include tampons and household and hospital grade disinfectants. Other therapeutic goods continue to be regulated as either 'registrable' or 'listable' goods, with the same TGA pre-market evaluation and manufacturer licensing requirements and procedures as previously (Sections 25, 26, 35 and 36 of the Act).

NOTE: *In-vitro* diagnostic devices (IVDs), devices of human origin and devices containing viable cells or tissue of animal origin are also regulated as 'other therapeutic goods'. Although these products fit the definition of a medical device, they have been excluded because the Australian Government is committed to developing new regulatory frameworks for them. In the interim period these products will be regulated as 'other therapeutic goods'

Principal investigator - see ' Investigator', above

Protocol

A document that provides the background, rationale and objectives of the study and describes its design, methodology, organisation and the conditions under which it is to be performed and managed.

Sponsor of the trial

The sponsor of the trial is the company, institution or organisation, body or individual (enterprise) that takes overall responsibility for the conduct of the trial and usually initiates, organises and supports a clinical study of an investigational product in human subjects. If the investigator initiates and organises the trial, he or she is to be defined as the sponsor of the trial and will be responsible for the sponsor's functions. This includes where another party (usually a pharmaceutical company) provides the medicinal product used in the clinical trial but has no other involvement in the conduct of the trial. The sponsor of the trial should be an Australian company or individual.

Trial site

The location where trial-related activities are actually conducted. See also composite trial site.

Unapproved therapeutic goods

Therapeutic goods (medicines, 'other therapeutic goods' and medical devices) that are not entered on the Australian Register of Therapeutic Goods.

APPENDIX 2

NOTIFICATION OF INTENT TO SUPPLY UNAPPROVED THERAPEUTIC GOODS UNDER THE CLINICAL TRIAL NOTIFICATION (CTN) SCHEME

(CTN FORM)

See: http://www.tga.gov.au/industry/clinical-trials-forms-ctn.htm

APPENDIX 3

CLINICAL TRIAL COMPLETION ADVICE

CTN AND CTX SCHEMES

See: http://www.tga.gov.au/industry/clinical-trials-forms-ctn.htm
or: http://www.tga.gov.au/industry/clinical-trials-forms-ctx.htm

APPENDIX 4

SUPPLY OF UNAPPROVED THERAPEUTIC GOODS UNDER THE CLINICAL TRIAL EXEMPTION (CTX) SCHEME

PART 1 THE CTX APPLICATION

PART 2 NOTIFICATION OF THE CONDUCT OF A TRIAL UNDER A CTX APPROVAL

See: http://www.tga.gov.au/industry/clinical-trials-forms-ctx.htm

APPENDIX 5

PARTICULARS OF THE PRODUCT AND TRIAL CLINICAL TRIAL EXEMPTION (CTX) SCHEME

PARTICULARS OF THE PRODUCT AND TRIAL
CLINICAL TRIAL EXEMPTION (CTX) SCHEME

Suggested format for medicines

The information to be included in Part 1 of the application should be compiled in accordance with the following format. Alternatively, sponsors may submit a completed form MLA164 as submitted to the UK Medicines Control Agency for a UK CTX application.

1. Name of product and strength

2. Description of pharmaceutical form (eg tablets, slow release tablets, capsules etc)

3. Active constituents. For each active constituent give:
   i. Name
   ii. Specification
   iii. Quantity/dose unit or %quantity
   iv. Unit

   in a column format.

   Notes:
   - include details of any overages
   - give constituents as actual substances included in the formulation eg as a salt and then as the base equivalent where applicable
   - use approved abbreviations for specifications (*see notes at end)
   - for liquid preparations, all quantities for oral preparations should relate to 5ml dosage. Please state any deviation from this rule. For other liquid preparations, including parenterals, express quantities as a percentage and insert WW, WV etc as appropriate in the unit column
   - see TGA approved terminology for unit abbreviations
   - trailing zeros following the decimal point may be omitted

4. Anticipated clinical use and proposed route(s) of administration

5. Dosage range and duration proposed in the Usage Guidelines

6. Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture

7. Other constituents. For each other constituent give:

   i. Name
   ii. Specification reference
   iii. Quantity/dose unit or %quantity
   iv. Unit

   in a column format.

Notes:
- clearly separate different components of the dosage form eg capsule shell components, coating components
- used approved abbreviations for specifications (*see notes at end)
- in the modifier column insert
  - **TO** if final volume cannot be expressed as a complete quantity
  - **ND** for substances not detectable in the final formulation eg solvents
  - **QS** if quantity not fixed eg for substances used to adjust pH
- for liquid preparations, all quantities for oral preparations should relate to 5ml dosage. Please state any deviation from this rule. For other liquid preparations, including parenterals, express quantities as a percentage and insert WW, WV etc as appropriate in the unit column
- see TGA approved terminology for unit abbreviations
- trailing zeros following the decimal point may be omitted

8. Description of essential processes in the manufacture

9. Finished product specification

10. Type of container(s), pack size, shelf life and storage precautions

11. Assemblers

12. Importers

13. Name(s) of manufacturer(s) and site(s) of manufacture of
    a. the active substance(s)
    b. the dosage form

14. Site and arrangements for quality control

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* The following format and abbreviations should be used for specification references:
- Abbreviations: BP, INN, BPC, USP, NF, FRP, DAB, IP, NDP, JAP, PHV, BHP
- where a specification reference does not refer to the latest published monograph, the relevant year should be given
- where an ingredient has no official monograph, please write HSE

Suggested format for medical devices

The information to be included in Part 1 of the application should be compiled in accordance with the following format.

1. Name of product
2. Description of the device
3. Design details and risk analysis
4. Mode of action and application
5. Anticipated method of clinical use
6. Materials, including biocompatibility
7. Toxicology
8. Name(s) of manufacturer(s) of the device and site(s) of manufacture

APPENDIX 6

DOCUMENTS FOR ETHICS COMMITTEES

APPENDIX 6

Document 1

SUMMARY STATEMENT
CLINICAL TRIAL EXEMPTION (CTX) SCHEME

For medicines:

1. Name and address of sponsor

2. Date of application to TGA

3. Generic name, dosage form and strength of each product to be used. For injectables, state whether a powder for reconstitution or a solution.

4. For all products state the route of administration and the dose or range of doses to be used.

5. Pharmacological class
   Other activities observed

For medical devices:

1. Name and address of sponsor

2. Date of application to TGA

3. Device name, concept, biomaterial content and biocompatability.

4. State the intended performance of the device and how it will be used

APPENDIX 6

Document 2

OVERSEAS STATUS
CLINICAL TRIAL EXEMPTION (CTX) SCHEME

Suggested format for CTX applications for medicines and medical devices

1. Sponsor

2. Date of Preparation

3. Date of amendment

4. Drug name/Device name (as appropriate)

5. i. Summary tabulation of status

	IND*		NDA*	
	Submitted mm/yy	Approved mm/yy	Submitted mm/yy	Approved mm/yy
UK**				
USA				
Sweden				
Canada				
New Zealand				

* IND Investigational New Drug Application
NDA New Drug Application (for General Marketing)

** If submitted in UK, indicate whether CTX or CTC route

ii. State if authorities in any of these countries have raised objections to the CTX, rejected NDA or INDs, or withdrawn approval on the advice of an agency or the sponsor

APPENDIX 6

Document 3

USAGE GUIDELINES – MEDICINES
CLINICAL TRIAL EXEMPTION (CTX) SCHEME

1. Sponsor
2. Date of Preparation
3. Date of amendment
4. Drug Name (Generic/Code Name/AAN)
5. Proposed indications
6. Age range
7. Dose form
8. Strengths
9. Regimen: specify route of administration, maximum daily dose and maximum duration
10. Inclusion criteria
11. Exclusion criteria
    i. identified by the class of compound
    ii. specific to the medicine. This may be due to observations in preclinical studies or the absence of certain preclinical data.
12. Safety monitoring
    i. routine haematology, biochemistry etc
    ii. related to class of drug
    iii. related to preclinical and/or safety data in earlier clinical studies*
13. TGA comment

* Special monitoring in paragraph iii may not be required and may not be appropriate in all trials. For the purpose of this document, the nature of any special monitoring should be stated. Wherever possible, it should also state whether any special monitoring data are being gathered in other centres.

APPENDIX 6

Document 4

USAGE GUIDELINES - MEDICAL DEVICES
CLINICAL TRIAL EXEMPTION (CTX) SCHEME

1. Sponsor

2. Date of Preparation

3. Date of amendment

4. Device Name

5. Proposed indications

6. Age range

7. Describe how the device will be used

8. Inclusion criteria

9. Exclusion criteria

    i. identified by the class of device
    ii. specific to the device. This may be due to observations in preclinical studies or the absence of certain preclinical data.

10. Safety monitoring

    i. related to class of device
    ii. related to preclinical and/or safety data in earlier clinical studies*

11. TGA comment

* Special monitoring in paragraph ii may not be required and may not be appropriate in all trials. For the purpose of this document, the nature of any special monitoring should be stated. Wherever possible, it should also state whether any special monitoring data are being gathered in other centres.

APPENDIX 7

ADRAC BLUE CARD

See: http://www.tga.gov.au/safety/problem-medicine-forms-bluecard.htm

APPENDIX 8

MEDICAL DEVICE INCIDENT REPORT FORM

See: http://www.tga.gov.au/safety/problem-device-report-user.htm

Therapeutic Goods Administration

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