



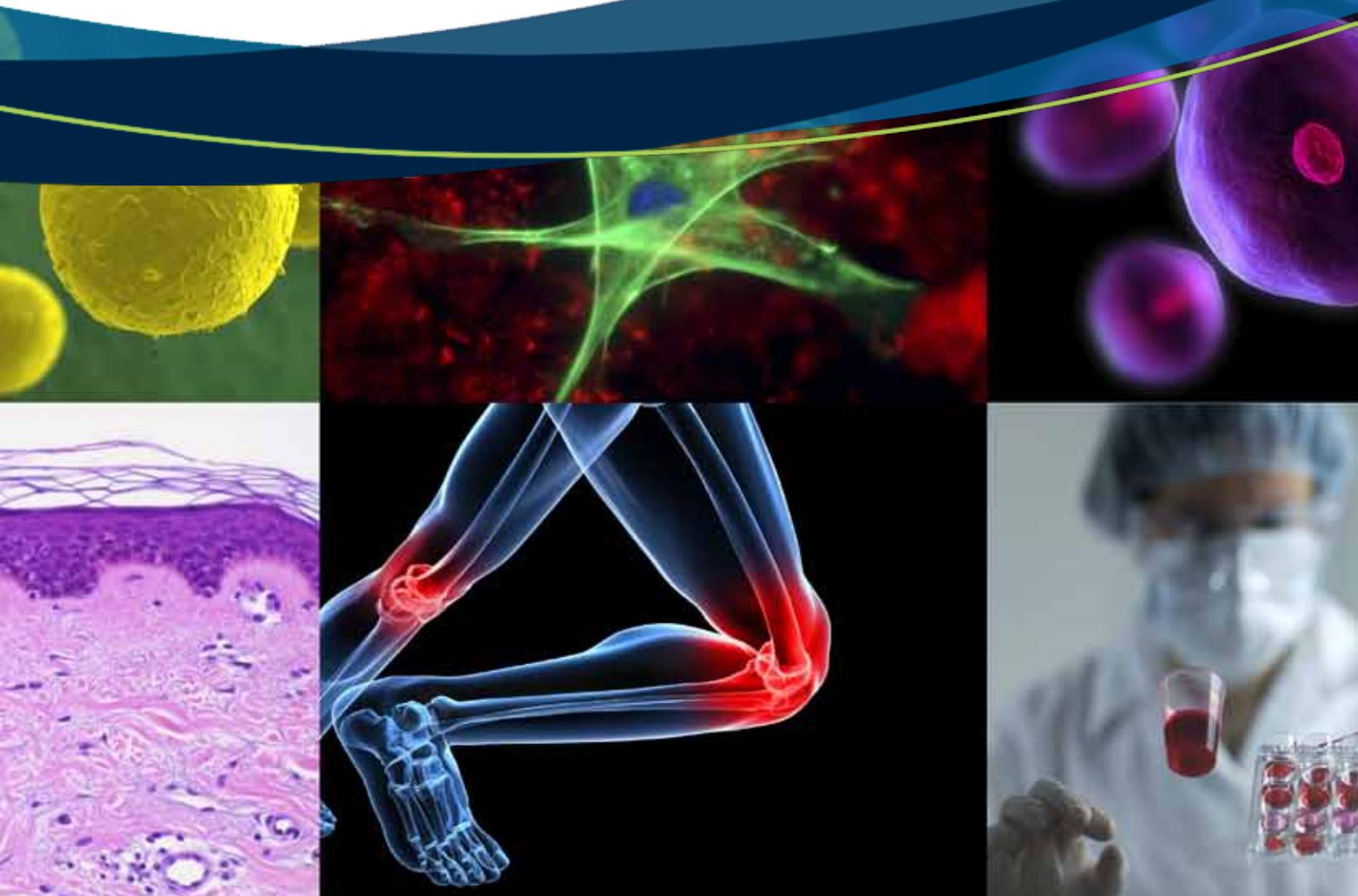
**Australian Government**  
**Department of Health and Ageing**  
Therapeutic Goods Administration

# Australian Regulatory Guidelines for Biologicals

## Part 3 - Access to unapproved biologicals

Version 1.0, June 2011

**TGA** Health Safety  
Regulation



## About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating biologicals, 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 biologicals, medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with biologicals, medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a biological, medicine or medical device, please see the information on the [TGA website](#).

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## Version history

Version	Description of change	Author	Effective date
V1.0	Original	BSS	June 2011

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# 3.1 Overview

Under the *Therapeutic Goods Act 1989* (TG Act), biologicals can be used in a number of specific situations without the usual process of evaluation and approval for inclusion on the Australian Register of Therapeutic Goods (ARTG). These exempt uses include:

- specific exemptions:
  - Special Access Scheme (SAS; such as for seriously ill patients)
  - through an authorised prescriber (where authorised medical practitioners can authorise use of a particular exempt biological without previous approval from the Therapeutic Goods Administration [TGA])
  - personal importation (where individuals can import a biological from overseas for their personal use, or for an immediate family member)
- special and experimental use (includes the Clinical Trial Notification and Clinical Trial Exemption schemes).

**See Part 1, Section 1.3 for further information about exempt uses of biologicals**

This part of the *Australian regulatory guidelines for biologicals* provides further information about each of these exempt uses that is relevant for biologicals.

All unapproved biologicals that fall under the specific exemptions are subject to the conditions specified in the Therapeutic Goods Regulations (TG Regulations), as well as any conditions that are specified in the notice of approval.

## 3.2 Specific exemptions

### 3.2.1 Special Access Scheme

The SAS allows an unapproved biological to be imported or supplied for a single patient, on a case-by-case basis.

For further information about the SAS, see the [TGA website](#).

Two types of patients can benefit under the SAS:

- **Category A patients** are those who are seriously ill, those for whom death is likely to occur within months, or those who have a condition where premature death is likely if treatment is not provided.
- **Category B patients** are those who fall outside the definition of a Category A patient.

Consumers, medical practitioners and the TGA all have certain rights and responsibilities under the SAS:

- Rights of the patient include
  - to have access to unapproved biologicals (e.g. for seriously ill patients), including biologicals that have been withdrawn from the Australian market for commercial or other reasons, biologicals provided to patients through a clinical trial while a marketing application is undergoing consideration, and biologicals available overseas but not marketed in Australia
  - to give informed consent.
- Responsibilities of the medical practitioner (prescriber) include
  - to classify patients as Category A or Category B
  - to provide information about benefits and risks, and alternative treatments, and obtain informed consent from the patient
  - to report adverse reactions.
- Responsibilities of the sponsor (supplier) include
  - to provide six-monthly reports
  - to monitor safety and use
  - to report adverse reactions.
- Responsibilities of the TGA include
  - to determine SAS requests
  - to encourage the use of approved biologicals.

For further information about the rights and responsibilities under the SAS, see the [TGA website](#).

## Arrangements for supply for Category A and Category B patients

If the biological is available from a supplier in Australia, the TGA recommends that the medical practitioner or authorised prescriber (see below) contacts the sponsor to arrange supply. The supplier will require authorisation to lawfully release the biological.

If a biological is not available from an Australian sponsor, the prescriber must find an overseas source and arrange importation.

### **Category A**

Supply of a therapeutic good for Category A patients requires notification of the TGA within 28 days of supply. To prescribe an unapproved biological for a category A patient, the medical practitioner must submit a completed *Category A form Special Access Scheme* to the sponsor and a copy to the TGA within 28 days, for notification purposes.

**The Category A Form is available on the [TGA website](#)**

### **Category B**

SAS supply for a Category B patient requires prior approval by the TGA. Applications must be made to the TGA using the *Special Access Scheme (SAS) request for Category B patients*.

**The Category B Form is available on the [TGA website](#)**

The medical practitioner needs to seek the approval of a 'delegate' authorised under the TG Act. This can either be a delegated medical officer within the TGA or a medical practitioner outside the TGA (e.g. in a hospital). For Category B patients, a letter from the TGA with the issued approval number will be sent to the requesting doctor. Generally, a decision will be made within two working days.

A written consent form is needed for biologicals as part of all Category B applications.

**The consent form is available on the [TGA website](#)**

Applications to delegated medical officers within the TGA need to be made by fax or in writing.

External delegates are based within some hospitals and are authorised to approve a small number of therapeutic goods. Medical practitioners first need to submit an inquiry in writing to a hospital's medical superintendent or chief pharmacist to determine whether a particular hospital has a local delegate.

Medical practitioners must provide the delegate with information about the patient, biological and prescriber, to use in deciding whether to approve supply to a Category B patient.

Table 3.1 summarises the information that the TGA requires to process applications for Category B patients under the SAS.

**Table 3.1 Information required by the TGA for applications involving Category B patients**

The patient	
Patient details	Initials, date of birth (or age), sex, patient ID or unit record number (if applicable), diagnosis, previous approval numbers for that patient (if applicable).
Clinical justification	An outline of the seriousness of the patient's condition, details of past treatment and, if other approved treatments are available, justification for the use of the unapproved biological in preference to those treatments.
The biological	
Product details	Product description.
Administration and monitoring regime	Dosage, route of administration, duration of treatment, details of proposed monitoring.
Efficacy and safety data	Efficacy and safety data sufficient to support the proposed use of the biological. A copy of the reference articles from which the data have been obtained should be included.
The prescriber	
Details	Name, postal address, phone number, fax number.

### Reporting adverse events

Under the SAS, the treating medical practitioner is responsible for reporting to the TGA any adverse reactions associated with the use of an unapproved biological.

Sponsors should also report to the TGA all serious and unexpected adverse reactions of which they have been informed, especially those that affect the risk-benefit assessment, and any information that may lead to changes in the use of the product. Fatal and life-threatening outcomes should be reported within seven calendar days of first knowledge, and followed up with a more comprehensive report within eight days of submitting the initial report.

For further information about reporting adverse reactions, see the [TGA website](#)

## 3.2.2 Authorised prescribers

An authorised prescriber is a medical practitioner whom the TGA has granted authority to prescribe a specific unapproved biological to specified patients, or classes of patients (identified by their medical condition).

For further information about authorised prescribers, see the [TGA website](#).

Once they become an authorised prescriber, the medical practitioner can prescribe that biological for the particular condition ('indication') to individual patients in their immediate care, without further approval from the TGA. Authorised prescribers can only supply the particular biological directly to the specified patient. They cannot supply the biological to other medical practitioners.

Medical practitioners who wish to become authorised prescribers must be endorsed by an ethics committee (e.g. the ethics committee of the hospital in which they practise, or any other appropriate ethics committee). Medical practitioners who do not have access to an ethics committee may be endorsed by an appropriate specialist college.

The rights and responsibilities of the patient, the authorised prescriber, the TGA and the sponsor are the same as described in [Section 3.2.1](#) for the Special Access Scheme

## Releasing information

The TGA will treat any information that it receives on the use of unapproved biologicals as confidential. Under the *Freedom of Information Act 1982*, consultation must occur between the TGA and the owners of the information before the documentation can be released. In addition, the *Privacy Act 1988* limits the disclosure of personal information by parties in possession or control of records.

### 3.2.3 Personal importation

Personal importation occurs when:

- an individual either brings a biological into Australia on their person or arranges from within Australia for a biological to be sent to them from an overseas supplier

and

- the biological is to be used by that individual or a member of their immediate family, and not sold or supplied to any other person.

Under these arrangements, personal importers need two permissions: permission to import, and permission to supply in Australia.

**For further information about personal importation, see the [TGA website](#)**

Quarantine clearance must be obtained before any material of biological origin (human, animal, plant or bacterial) is imported. The importer should contact the [Australian Quarantine and Inspection Service \(AQIS\)](#) to see whether an import permit is required.

Importation of biologicals under this scheme is also subject to a number of conditions and responsibilities.

#### ***Responsibility of the personal importer***

People wishing to import unapproved biologicals for their personal use should be aware that, in many cases, the quality, safety and efficacy of the goods may be unknown. Therefore, they must be prepared to accept any risks associated with the use of such products. If an individual suffers adverse consequences from using such biologicals, information about the goods and redress may be difficult to obtain. The quantity imported cannot exceed 3 months' supply per importation, and the total quantity imported each year cannot exceed 15 months' supply at the manufacturer's recommended maximum dosage. Individuals cannot import:

- injections that contain substances of human or animal origin (except insulin) without an SAS approval
- medical devices using tissues, cells or substances of animal origin (nonviable), or bacterial or recombinant origin
- products incorporating or intending to incorporate derivatives of human blood or blood plasma.

These products represent a high risk and approvals will only be given to the supervising physician by the TGA.

## 3.3 Clinical trials

Access to biologicals for use in clinical trials can fall under one of two schemes:

- Clinical Trial Notification Scheme (CTN)
- Clinical Trial Exemption Scheme (CTX).

The schemes apply to the testing of any biologicals not entered on the ARTG, including any new preparations or uses, as well as use of an included biological in a clinical trial beyond the conditions of its marketing approval. The clinical trial arrangements (for both schemes) are based on the same risk-management principles that apply to medicines and medical devices (but with particular arrangements for higher risk biologicals). Special arrangements apply to clinical trials that are already under way.

All trials run under the CTN and CTX schemes must have an Australian sponsor.



### Clinical trial sponsor

The sponsor is that person (e.g. medical practitioner), body, organisation (e.g. pharmaceutical company) or institution (e.g. hospital) that takes overall responsibility for running the trial, and signs either the Clinical Trial Notification Scheme form or the Clinical Trial Exemption Scheme form.

The sponsor usually initiates, organises and supports a clinical trial, and carries the medicolegal responsibility associated with running the trial. The responsibilities of sponsors are outlined in Section 5 of the CPMP/ICH *Note for guidance on good clinical practice* (CPMP/ICH/135/95), which is available on the [TGA website](#). Sponsors must also comply with state and territory legislation.

A clinical trial of a biological could be either CTN or CTX.

The CTX Scheme is mandatory for a trial of any Class 4 biological unless:

- Use of the biological is supported by evidence from previous clinical use; or
- Has received clinical trial approval for an equivalent indication from a national regulatory body with comparable regulatory requirements.

The sponsor is responsible for initially deciding whether a trial should be run under a CTN or CTX scheme. They forward their application to the relevant human research ethics committee (HREC) who reviews the protocol, including the suggested scheme classification. If the HREC supports the current protocol and classification, the HREC provides advice to the 'approving authority', which decides whether the trial should be run. Alternatively, the HREC may recommend the trial be run under the alternative scheme.

### 3.3.1 Clinical Trial Notification Scheme

The CTN Scheme allows access to unapproved therapeutic goods in special circumstances, without the need for prior approval from the TGA. Under the CTN Scheme, researchers submit all information on the proposed trial to their relevant HREC at the request of the sponsor. The HREC is responsible for assessing the scientific validity of the trial design, the safety and efficacy of the biological, the ethical acceptability of the trial process and finally approving the trial protocol. The institution where the trial will be conducted gives the final approval for conducting the trial at the site, taking into account the advice from the HREC. CTN Scheme trials cannot begin until the TGA has been notified (using the *Notification of intent to supply unapproved therapeutic goods under the Clinical Trial Notification [CTN] Scheme form*), and the appropriate notification fee has been paid (see Table 3.2). A new CTN form must be completed when

there is a substantial change in the protocol, leading to a change in the HREC approval or the addition of new, unapproved biologicals to the trial.

At the end of the trial, a *CTN clinical trial completion advice form* must be completed and submitted to the TGA.

**Further information about the CTN Scheme and the CTN application and completion forms are available on the [TGA website](#).**

### 3.3.2 Clinical Trial Exemption Scheme

The CTX Scheme provides access to unapproved therapeutic goods after the TGA has assessed relevant data and approved the use of the biological for clinical trials.

The CTX Scheme is mandatory for clinical trials that use Class 4 biologicals (i.e. those that have the highest risks), unless the criteria noted in 3.3 above are met. The sponsor must submit an application for a clinical trial to the TGA for evaluation. The TGA delegate (either internal or external) decides whether the application is acceptable. If not, the trial cannot proceed until the sponsor has addressed the objection to the delegate's satisfaction. Under the CTX Scheme, sponsors cannot begin a clinical trial until they have received written advice from the TGA about their application, approval from their relevant HREC and approval from the institution in which the trial will be run.

Sponsors must submit two separate forms to the TGA, the formal CTX Scheme application (*Supply of unapproved therapeutic goods under the clinical trial exemption (CTX) scheme - Part 1 The CTX application*) and the form that notifies the TGA of each new trial commencement. The former must be accompanied by the evaluation fee (see Table 3.2); the latter must be submitted within 28 days of the trial starting and there is no further fee.

At the end of the trial, a *CTN or CTX Clinical Trial Completion Advice Form* must be completed and submitted to the TGA.

**Further information about the CTX Scheme and the CTX application and completion forms are available on the [TGA website](#).**

### 3.3.3 Conditions applying to trials under the CTX scheme

The TGA may grant approval subject to any conditions specified in the notice of approval.

The use of a biological for experimental purposes in humans is subject to the conditions (if any) specified in the regulations relating to one or more of the following:

- preconditions on the use of the biological
- principles to be followed in the use of the biological
- monitoring of the use and the results of use of the biological
- circumstances under which the experimenter must cease the use of the biological.

### 3.3.4 Making the application

The CTN scheme requires only notification to TGA, and is not subject to TGA approval. However, a correctly completed *Notification of Intent to Supply Unapproved Therapeutic Goods Under the Clinical Trial Notification [CTN] Scheme Form*, accompanied by the appropriate fee, must be received by the TGA before the trial can begin.

A correctly completed application for an approval under the CTX scheme must be made to the TGA on the form *Supply of unapproved therapeutic goods under the clinical trial exemption (CTX) scheme - Part 1 The CTX application*, and contain information on the biological as is required by the TGA. The application must be accompanied by the prescribed evaluation fee (see Table 3.2).

The TGA, after evaluating the information, must notify the applicant of the decision on the application and notify them of the reasons if approval is not granted.

**Table 3.2 Fees for clinical trials**

Clinical trial scheme	Method of recovery	Basis of charge	Fee (\$)
Clinical trial notification	Fee for service	Per application	280
Clinical trial exemption—assessment of data	Fee for service	Per application	21,600

Note: These fees are correct at the time of publication (31 May 2011). Refer to the TG Regulations, schedule 9 for the current fees.

### Timelines

The CTN Scheme is a notification scheme, so there is no statutory time frame. However, the trial cannot proceed until notification has been received.

The CTX Scheme requires evaluation by the TGA. Initial evaluation has a time frame of 50 working days; variations to the trial protocol have a time frame of 30 working days.

For further information about the CTN and CTX schemes, see the [TGA website](#).

## 3.3.5 Reporting adverse reactions arising during clinical trials

The TGA takes reporting adverse events relating to unapproved biologicals used in clinical trials very seriously. Sponsors should read the '*Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)*', which has been adopted under the Therapeutic Goods Regulations by Australia. The TGA has also 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.

These documents are available on the [TGA website](#).

## 3.4 References

Resource	URL
TGA website	<a href="http://www.tga.gov.au/">http://www.tga.gov.au/</a>
Special Access Scheme	<a href="http://www.tga.gov.au/hp/access-sas.htm">http://www.tga.gov.au/hp/access-sas.htm</a>
Reporting adverse reactions	<a href="http://www.tga.gov.au/safety/problem-medicine.htm">http://www.tga.gov.au/safety/problem-medicine.htm</a>
Authorised prescribers	<a href="http://www.tga.gov.au/hp/access-authorised-prescriber.htm">http://www.tga.gov.au/hp/access-authorised-prescriber.htm</a>
Personal Importation	<a href="http://www.tga.gov.au/consumers/personal-importation-scheme.htm">http://www.tga.gov.au/consumers/personal-importation-scheme.htm</a>
AQIS	<a href="http://www.daff.gov.au/aqis">http://www.daff.gov.au/aqis</a>
CPMP/ICH <i>Note for guidance on good clinical practice</i> (CPMP/ICH/135/95)	<a href="http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm">http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm</a>
CTN Scheme and the CTN application and completion forms	<a href="http://www.tga.gov.au/hp/clinical-trials.htm">http://www.tga.gov.au/hp/clinical-trials.htm</a>
CTX Scheme and the CTX application and completion forms	<a href="http://www.tga.gov.au/hp/clinical-trials.htm">http://www.tga.gov.au/hp/clinical-trials.htm</a>
Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)	<a href="http://www.tga.gov.au/pdf/euguide/ich37795.pdf">http://www.tga.gov.au/pdf/euguide/ich37795.pdf</a>

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