



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Module 1

Administrative Information and Prescribing Information

For Australia

Notice to Applicants
CTD-Module 1
TGA Edition November 2008

DOCUMENT CHANGE RECORD

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ABBREVIATIONS AND ACRONYMS

AAN	Australian Approved Name
AAT	Administrative Appeals Tribunal
ADEC	Australian Drug Evaluation Committee
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods (the Register)
CEP	Certificate of Suitability (Ph Eur monograph)
CMI	Consumer Medicine Information
CHMP	Committee for Medicinal Products for Human Use (formally, Committee for Proprietary Medicinal Products) (EU)
CTD	Common Technical Document
DMF	Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FOI	Freedom of Information
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GTRAP	Gene and Related Therapies Research Advisory Panel
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IPD	Individual Patient Data
IT	Information technology
JETACAR	Joint Expert Technical Advisory Committee on Antibiotic Resistance
MTES	Medicines Toxicology Evaluation Section
NHMRC	National Health and Medical Research Council
OGTR	Office of the Gene Technology Regulator
OPM	Office of Prescription Medicines
OMQ	Office of Manufacturing Quality
PAR	Provisional ARTG Record
PCES	Pharmaceutical Chemistry Evaluation Section
pdf	portable document format
PI	Product Information
PMF	Plasma Master File
RMP	Risk Management Plan
SAN	Self-Assessment Notification
SmPC	Summary of Product Characteristics (European)
TGA	Therapeutic Goods Administration
TGO	Therapeutic Goods Order
UK	United Kingdom
USA	United States of America

INTRODUCTION

This guideline provides recommendations for applicants preparing a Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the Therapeutic Goods Administration (TGA). The document describes how to organise applications based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on the CTD.

According to the CTD format, each application is a collection of documents, grouped into 5 modules. This guideline provides information on the contents of *Module 1: Administrative Information and Prescribing Information*, which is region specific. The *Notice to Applicants: Medicinal products for human use. Volume 2B: Presentation and format of the dossier CTD (July 2003)*¹ describes the format and organisation of the Summaries, Quality, Non-clinical, and Clinical modules (Modules 2 to 5, respectively).

The CTD guidelines, together with the *Australian Regulatory Guidelines for Prescription Medicines*² (ARGPM) and the technical guidelines³, provide detailed information about the contents of an application. These guidelines apply to applications to register medicines and all related variations. Applicants should not modify the overall organisation of the CTD.

If not contained in the bulk of the documentation, any additional data should be included as addenda to the relevant part, together with additional expert comment that may be provided as a supplement to, or incorporated into, the relevant summary, overall summary or overview.

Module 1 - Administrative information and prescribing information

Relevant administrative documentation should be submitted in Module 1 of the CTD dossier. This module should be divided into the relevant sections, as described in Part B of this guideline.

Module 2 - Summary of the dossier

Module 2 of the CTD dossier contains the summaries and overviews for the quality, non-clinical and clinical sections of the dossier (refer to *Notice to Applicants: Medicinal products for human use. Volume 2B: Presentation and format of the dossier CTD (July 2003)*¹).

The *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)*⁴ states "Clinical trials should be conducted in accordance with the ethical principles that have their origin

¹ <http://www.tga.gov.au/docs/html/eugctd.htm>

² <http://www.tga.gov.au/pmeds/argpm.htm>

³ <http://www.tga.gov.au/docs/html/euguideh.htm>

⁴ <http://www.tga.gov.au/docs/pdf/euguide/ich/ich13595.pdf>

in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)." For trials conducted in Australia applicable regulatory requirements include the National Health and Medical Research Council (NHMRC) *National Statement on Ethical Conduct in Research Involving Humans*⁵. The Clinical Overview should include a statement regarding GCP compliance.

Module 3 – Quality

Module 3 of the dossier contains the chemical, pharmaceutical and biological data relevant to the application.

The sponsors (*open*) part of a DMF should be included in Module 3.2.S of Module 3. A copy of the Letter of Access to the active substance manufacturer's restricted (*closed*) part of the DMF should be included in Module 1.6.3.

The Drug Substance module of Module 3 should refer to the Certificate of Suitability in the relevant sub-sections of Module 3.2.S. Complete copies of the Certificates of Suitability (including any annexes) should be provided in Module 1.6.4 and Module 3.2.R.

Full reports on biopharmaceutical studies, including methodology and validation data for bioavailability studies, should be included in Module 5.3.1. An additional copy of this module should be submitted for evaluation by the Pharmaceutical Chemistry Evaluation Section (PCES).

Module 4 - Non-clinical study reports

Module 4 of the dossier contains the non-clinical (pharmaco-toxicological) data relevant to the application.

Module 5 - Clinical study reports

Module 5 of the dossier contains the clinical data relevant to the application.

In most circumstances, the clinical studies included in Module 5 of the dossier will be international studies used to establish the pharmacodynamics, pharmacokinetics, safety and efficacy of the medicine across an international patient population. However, where there is evidence to suggest that the pharmacokinetics or pharmacodynamics of the product may vary across the populations that will use the medicine in Australia, the sponsor should consider submitting studies relevant to those target populations.

European Union guidelines on quality, safety and efficacy

The technical content of the documents in the CTD modules is outside the scope of this guidance. The CTD guidelines do not indicate the data or studies required; they merely indicate an appropriate format and organisation for the data that have been acquired.

⁵ <http://www.nhmrc.gov.au/publications/synopses/e35syn.htm>
CTD, Module 1, TGA, November 2008

The technical data requirements for the registration of medicines evaluated by the Office of Prescription Medicines (OPM) of the TGA have been closely aligned with those of the European Union (EU). Guidelines prepared by the European Committee for Medicinal Products for Human Use (CHMP) and/or those prepared within the ICH process are considered within the Australian regulatory/legislative environment before a decision is made with regard to their suitability for adoption in Australia.

The EU guidelines evolve over time and additions and revisions may be adopted in Australia. As each new guideline or revision is adopted in the EU, it is assessed, in consultation with Australian industry, to determine if it should be adopted in Australia, including whether or not previous guidelines need to be updated or replaced. The outcome of this assessment will be published on the TGA website. For a small number of the EU guidance documents that have been adopted in Australia, additional TGA comments are provided. These comments are noted on the TGA website listing of adopted EU guidelines.

Sponsors should note that the Annexes to Modules 3, 4 and 5 of the EU CTD have not been adopted in Australia. These Annexes contain lists of CHMP Guidelines adopted in the EU. A complete list of the CHMP Guidelines adopted by the TGA is published on the TGA website³.

PART A: GENERAL INFORMATION FOR APPLICATIONS

1. Letter of Application

Sponsors should include a *Letter of Application* with all applications. A copy of the letter should be placed in Module 1.0.

2. Language

Information supporting an application must be in English and legible. Where material is not originally in English, a copy in the original language and a full translation should be submitted, the accuracy of which is the responsibility of the sponsor. Reports submitted only in a language other than English will not be accepted.

3. Preparing and organising the Common Technical Document

To facilitate the review of the basic data and to help an evaluator become oriented with the application contents, the display of information should be unambiguous and transparent throughout the CTD.

The CTD format should be used for applications whether or not any previous application was in the CTD format. In exceptional circumstances TGA may consider, on a case-by-case basis, accepting applications in the US version of the CTD format, rather than the EU version of the CTD format. This should be discussed at a pre-submission meeting (see Section 3.1.1 of the *ARGPM*⁶).

If additional or supplementary data are submitted, the module(s) should be identified and numbering should follow from the original documentation.

The CTD structure should be used for amendments and variations. The applicant should not submit the modules that are not used i.e. it is unnecessary to include “not applicable” pages against unused CTD headings.

A literature based submission should be prepared using the CTD format. The specific requirements for such applications are discussed in the document *Literature based submissions - points to consider*⁶ and Part B of this guideline (see Module 1.5.1).

Acronyms and abbreviations should be defined the first time they are used in each module.

⁶ <http://www.tga.gov.au/docs/html/litbsubs.htm>

4. Documentation

Copies of the documentation should be submitted in the following quantities:

Modules 1 & 2	4 copies numbered as copies 1 to 4.
Module 3	2 copies
Module 4	1 copy
Module 5	1 copy
Module 5.3.1 (Reports of Biopharmaceutic Studies)	1 extra copy ⁷
Module 5.3.2 (Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials)	1 extra copy

The submission of complete copies of the dossier using electronic storage media, in addition to hard copies (i.e. paper copies), is strongly encouraged. If submitting electronic copies of the dossier in addition to the normal paper requirements (above), please submit two complete electronic copies for each of the evaluation sections (quality, non-clinical and clinical) concerned⁸.

Applicants are advised that where an electronic application is submitted, the paper CTD remains the formal submission, and therefore both paper and electronic submissions must comply fully with the Common Technical Document as regards presentation and content of the dossier. Applicants must sign a letter in which they confirm that the data on the CD-ROM/DVD supplied is identical to that in the written submission.

5. Organising documents

Documents can be combined in volumes as long as they are separated by appropriately named tab identifiers. For example, the Product Information should be separated from the other documents by a tab identifier named *Product Information*. In general, documents from different CTD modules should not be included in the same volume. You may want to combine documents from different modules in the same volume for amendments consisting of a small number of short documents.

Administrative documents (for example, Letter of access to Drug Master Files, Statement on the availability of Individual Patient Data) are included in Module 1. The organisation of such documents should be consistent with the structure described in this guideline. Since these administrative documents are small, they should be placed

⁷ Module 5 contains the reports of biopharmaceutic studies (bioavailability and bioequivalence data) (Module 5.3.1) and studies pertinent to pharmacokinetics using human biomaterials (Module 5.3.2). Additional copies of these modules are included for evaluation by the PCES and Medicines Toxicology Evaluation Section (MTES), respectively.

⁸ Advice as to the possibility of submitting a reduced number of paper copies when accompanied by an electronic submission should be sought on case-by-case basis and should be discussed with OPM at least 5 weeks prior to the actual date of submission. In principle, applicants may submit to the TGA 6 full copies of the dossier on a suitable PC-compatible medium (CD-ROM or DVD) together with 1 additional paper copy of Modules 1 to 5.

in the same volume, separated by tab identifiers. If an environmental assessment and/or data on antibiotic resistance are submitted, they should be provided as separate volumes.

6. Size and binding

All data, including additional and supplementary data, and responses to Section 31 requests for further information which exceed 10 pages, submitted in support of an application should be bound. Binders with durable covers containing A4 paper, which can be dismantled and reassembled, are preferred. The external dimensions of the binders should not exceed 290 x 370 mm and 80 mm in thickness. The weight of any box in which data is submitted should not exceed 16kg.

7. Volume identification

Volumes must be numbered by module, resulting in a separate set of numbers for each module.

The labelling of each volume should include:

- Name of applicant
- Name of medicine
- Module and Volume number. The volumes in each module should be numbered separately and sequentially using the format: *x of y volumes*, where x is the number for the specific volume and y is the total number of volumes submitted for the respective module. For example, Module 3, Vol.1 of 6.
- Copy number. The 4 copies of Modules 1 and 2 and the 2 copies of Module 3 should be numbered as copies 1 to 4 and 1 and 2, respectively. The extra copies of Module 5.3.1 (Reports of Biopharmaceutic Studies) and Module 5.3.2 (Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials) should be clearly labelled as duplicate copies.
- Contents. Each volume must also be labelled according to the section(s), which it contains, for example: *Section 3.2.P.4*, meaning:

- 3. – Module 3 - Quality
 - 2. – Body of data
 - P. – Product
 - 4. – Control of excipients

8. Pagination

A document is a set of pages, numbered sequentially and divided from other documents by a tab. Page numbering should be at the document level and not at the volume or module level. (The entire submission should never be numbered consecutively by page.) In general, all documents should have page numbers. Since the page numbering is at the document level, there should only be one set of page numbers for each document.

Cross-referencing to documents should be made by referring to the CTD module, volume, tab identifier, and page number (for example, see Module 3, Vol. 6, P.4.3 Method validation, p 23).

You can submit documents printed on both sides of a page, provided legibility is not impaired and margin space is sufficient on both the left and right side, so that information is not obscured when the page is placed in a binder.

9. Paper size

Standard A4 paper should be used for all submissions. Text and tables should be prepared using margins that allow the document to be printed on A4 paper. The left-hand margin should be sufficiently large that information is not obscured through binding.

10. Fonts

Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying or when provided electronically. Generally, a font size of 10 points is considered acceptable in tables, but fonts smaller than 12 points should be avoided whenever possible. Times New Roman, 12-point font is recommended for narrative text. Ten-point font is recommended for footnotes.

PART B: MODULE 1

Module 1 should contain all administrative documents (for example, application forms and certifications), labelling, general correspondence and annexes (environmental assessments, antibiotic resistance and overseas evaluation reports), as needed. Documents should be organised in the order listed below. Generally, all of the documents in Module 1, other than the annexes, can be provided in a single volume. The annexes to the module should be submitted in separate volumes.

Module 1.0 Letter of Application

Use and disclosure of information and documents in registration applications

Documentation		
1.	1.0.1	Letter of Application
2.	1.0.2	Request for confidentiality (optional)

Sponsors should include a *Letter of Application* with all applications. A copy of the letter should be placed at the beginning of Module 1.

Sponsors sometimes request that information contained in their application remains confidential. Sponsors should be aware however, that the Department of Health and Ageing, which includes TGA, is under certain legal obligations and has certain legal rights with respect to the use and release of information submitted with applications. Therefore, any confidentiality claimed in respect of documents submitted with applications for registrations is not able to override these legal obligations and authorisations.

In respect of requests submitted pursuant to the *Freedom of Information Act 1982* (FOI Act), the Department of Health and Ageing is not the final arbiter of whether a document is exempt from disclosure. The Department's practice, consistent with the requirements of the FOI Act, is to consult with the sponsor who submitted the information claimed to be confidential, to:

- establish whether release of the information is possible, and
- give the sponsor the opportunity to request a review by the Administrative Appeals Tribunal (AAT) of any decision made by the TGA to release the sponsor's information under the terms of the FOI Act.

In addition to its obligations under the FOI Act, there are other lawful releases that TGA may make of information, provided for by the *Therapeutic Goods Act 1989* and other Commonwealth laws. The TGA will not comply with demands for undertakings of confidentiality, nor consider itself bound by statements as to confidentiality, which seek to limit the lawful use or release of information by the TGA. The TGA and the Australian Drug Evaluation Committee have a duty to evaluate therapeutic goods using all

information available to them to ensure public safety. Therefore, relevant information may be accessed and used subject to law. To carry out this function successfully, it is necessary that persons involved in the evaluation of registration applications have access to:

- all Departmental records of prior applications, and
- the accumulated knowledge and experience which has been gained from the evaluation of previous applications.

The seeking of confidentiality undertakings that purport to preclude such access is not acceptable. In the event of an FOI request, should a document or documents submitted with or as part of an application for registration appear to fall within one of the categories referred to in section 27 of the FOI Act, TGA follows the procedure for consultation required by s 27. Any views that a sponsor provides in that consultation process are taken into account, but are not necessarily binding on TGA.

All documents received with an application will be reproduced or copied in a manner consistent with TGA's lawful rights and obligations.

In relation to confidentiality statements previously submitted to TGA, it should be understood that the TGA does not accept these as binding on it, and they will be treated in the same manner as outlined above. The confidentiality statements were treated as indicia of what was regarded by sponsors as confidential, however whether that information is truly confidential, and TGA's legal obligations with respect to the information, take precedence over any claims made in the confidentiality statement.

Module 1.1 *Comprehensive table of contents*

Documentation		
1.	1.1	Comprehensive table of contents

Module 1 should include a comprehensive table of contents for the entire application. The comprehensive table of contents should include a complete list of all documents provided in the application by module.

In the table of contents, the location of each document should be identified by referring to the volume numbers that contain the relevant documents and any tab identifiers. In general, the name for the tab identifier should be the name of the document (for example, Provisional Australian Register of Therapeutic Goods (ARTG) Record) or section heading according to the CTD format (for example, 3.2.P.4.2). If the full name of the document is too long for the tab identifiers, an alternative name that adequately identifies the document should be substituted. Page numbers should not be used in the table of contents to refer to documents, rather; tab identifiers as described above should be used.

Module 1.2 Application form

Documentation		
1.	1.2.1	Application Form
2.	1.2.2	Application Form(s) for Proposing a Chemical Name

Module 1.2.1 Application form

An application to register a prescription medicine for human use in Australia must be accompanied by a completed application form⁹. The paper application form is available on the TGA website¹⁰.

The application form refers to a client ID code. If the sponsor and/or agent has been allocated a Client Identification code but you do not know it, please contact the ARTG Operations Manager to obtain it. If you have not been allocated a code, you will need to complete a separate *Client Details* form¹⁰. If an agent of the sponsor is handling the submission, an *Agent Authorisation* form (Section D of Client Details form) will need to be completed. These forms should be sent, with Part A of the *Application Form* to the Office of Financial and Property Services, TGA and should not be included in Module 1.

The application form includes a draft provisional ARTG record (PAR). The information included on the provisional record is updated as required during evaluation of the application. At the conclusion of the evaluation, the final information becomes the ARTG entry for the product.

Module 1.2.2 Proposing a new chemical name

Sponsors should use Australian Approved Name (AAN) terminology. For those ingredients without an AAN, an *Application Form for Proposing a Chemical Name*¹¹ should be completed and included in Module 1.2.3 of the CTD. The ARTG entry can only be finalised using AANs.

If the formulation includes a new Proprietary Ingredient, sponsors should complete the *Notification of a New Proprietary Ingredient* form¹². This form should be sent to the Proprietary Ingredient Coordination Unit, Office of Non Prescription Medicines, TGA and should not be included in Module 1.

⁹ TGA is developing an electronic application form for applications to register new or vary the registration of existing prescription and other high risk medicines evaluated by the Office of Prescription Medicines. Initially this will be available for applications to register new chemical entities and new generic medicines. If the sponsor completes an electronic version of the Application Form, rather than the paper version of the Application Form, please insert a printed copy of the electronic Application Form in module 1.2.1.

¹⁰ <http://www.tga.gov.au/docs/html/pmrvfom.htm>

¹¹ <http://www.tga.gov.au/docs/pdf/aanapp1.pdf>

¹² <http://www.tga.gov.au/docs/html/forms/notifpi.htm>

Module 1.3 Australian labelling and packaging

Documentation		
1.	1.3.1	Proposed Australian Product Information
2.		Annotated copy of proposed Australian Product Information
3.	1.3.2	Proposed Australian Consumer Medicine Information
4.	1.3.3	Declaration concerning the use of human embryos or human embryonic stem cells
5.	1.3.4	Mock-ups and specimens of proposed Australian Labelling OR, if not available , a text only version of the proposed labelling

Applicants should include the proposed texts of Product Information (PI) (Module 1.3.1) and Consumer Medicine Information (CMI) leaflets (Module 1.3.2). A brief description of the proposed packaging(s) of the product and the pack size(s) is to be included in the Provisional ARTG Record and described in detail in Module 3.2.P.7. Australian specific labels should be submitted in Module 1.3.4 (Mock-ups, specimens or text).

Package Inserts

The Act requires that the presentation of the goods be acceptable. This includes the labelling and the content of any package insert that will be supplied with the product. In general, a package insert does not require evaluation by the TGA. However, the TGA may review package inserts if they contain information relating to the safe and appropriate use of the goods. An example may be where obligatory labelling information does not fit on the label, and so is included in a package insert instead.

It is the sponsor's responsibility to ensure that all package inserts remain consistent with the label, PI and/or CMI, as appropriate. It is also important that package inserts be non-promotional.

The Product Information should be supplied as a package insert for products for parenteral use. However, for self-administered injections, the Consumer Medicine Information may be included as the package insert in addition to the PI.

Module 1.3.1 Proposed Australian product information

Module 1.3.1 should include a copy of the draft Australian PI. For details of the format and content of the PI, see Section 4.1.3.2 and Appendix 8 of the ARGPM².

For an application for the registration of a new medicine, the sponsor should also provide a copy of the proposed PI text with annotations directing evaluators to the information in the summaries and other modules that support the information in the PI. For other applications, only altered statements need be annotated.

It is a condition of registration under S28 of the *Therapeutic Goods Act 1989* that a PI be provided for each registered product. After registration, the PI must not be changed without TGA approval (except in the case of safety-related changes, see Section 4.4.5.1 of the ARGPM).

Module 1.3.2 Proposed Australian consumer medicine information

Module 1.3.2 should contain a copy of the draft Australian Consumer Medicine Information (CMI), also known as *Patient Information*. A copy of the draft CMI should be submitted with all applications that will result in a new ARTG entry.

For details of the format and content of the CMI, see Schedule 12 of the *Therapeutic Goods Regulations*. Sponsors should refer to Part 2A of Regulation 9A – Patient Information. The CMI must be written in easily understood English, be consistent with the PI document and include information under each of the headings listed in Schedule 12 of the *Therapeutic Goods Regulations*.

In addition to the requirements of the Regulations, sponsors are strongly encouraged to follow the usability guidelines *Writing about Medicines for People: Usability Guidelines for Consumer Medicine Information*, when developing a CMI. These guidelines outline the correct procedure for writing, testing, implementing and monitoring CMI. They also describe how to write CMIs in a way that will be most useful to, and easy to read by, consumers. In this way it is hoped that CMIs will provide useful and easy to understand information to help consumers to use their medicines wisely and get the most benefit from them.

Module 1.3.3 Therapeutic goods and use of human embryos or human embryonic stem cells or material derived therefrom

For products that are manufactured using a human embryo or a human embryonic stem cell, or any material sourced from a human embryo or human embryonic stem cell, there must be a statement of origin in the PI and the CMI.

Applications resulting in a new registration in the ARTG must include a declaration concerning the use of such material as part of Module 1.3.3.

Sponsor Declaration

In relation to this submission, I certify that to the best of my knowledge:

- A
- i The goods that are the subject of this submission are/are not (delete whichever is not applicable) manufactured using a human embryo or human embryonic stem cell, or other material sourced from a human embryo or human embryonic stem cell;
 - ii The draft PI and CMI do/do not (delete whichever is not applicable) include a statement that human embryos or human embryonic stem cells or any other material sourced from a human embryo or human embryonic stem cell were used in the manufacture of the therapeutic good.
- B
- i Information included in this submission does/does not (delete whichever is not applicable) refer to the use of human embryos, human embryonic stem cells (or materials sourced from human embryos or human embryonic stem cells) in research undertaken in the development of the medicine.

If this answer is affirmative, list references¹³ below:

- ii The draft PI and CMI do/do not (delete whichever is not applicable) include a statement that human embryos, human embryonic stem cells (or materials sourced from human embryos or human embryonic stem cells) were used in research undertaken in the development of the medicine.

Signature:

Date:

	/		/	
dd		mm		yy

Name:

(please print)

Position/ Relationship to
Sponsor:

(Declaration must be signed by an authorised officer of the company)

¹³ Cross-referencing to documents should be made by referring to the CTD module, volume and tab identifier

Module 1.3.4 Mock-ups and specimens

The Therapeutic Goods Order *General Requirements for Labels for Medicines* (TGO 69)¹⁴ must be complied with unless otherwise exempted (see Section 2.5.5 in the ARGPM). Sponsors should also note that labelling should meet the requirements of other Commonwealth, State and Territory legislation.

If the product sponsor has a specimen or mock-up of the sales presentation of the medicine available at the time of initial application, it should be included in Module 1.3.4.

A *mock-up* is a copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging / labelling of the medicine. It is also referred to as a *paper copy* or *computer generated version*.

A specimen is a sample of the actual printed outer and inner packaging materials and package leaflet.

If there are multiple strengths and/or pack sizes, one representative specimen or mock-up will be sufficient. If batch number and expiry date are to be printed on the label during packaging, a statement to this effect should accompany the labels. If mock-ups or specimens are not available at the time of initial application, a text version may be submitted, however, mock-ups or specimens must be submitted to the TGA, during the evaluation process and prior to finalisation of the application.

¹⁴ <http://www.tga.gov.au/docs/html/tgo/tgo69.htm>
CTD, Module 1, TGA, November 2008

Module 1.4.1 Information about the experts

Documentation		
1.	1.4.1	Declaration signed by the expert - Quality
2.		Information about the Expert - Quality
3.	1.4.2	Declaration signed by the expert - Non-clinical
4.		Information about the Expert - Non-clinical
5.	1.4.3	Declaration signed by the expert - Clinical
6.		Information about the Expert - Clinical

In accordance with the European Union (EU) CTD, experts must provide detailed reports of the documents and particulars, which constitute Modules 3, 4 and 5.

The requirement for these signed Expert Reports may be met by providing:

- The Quality Overall Summary, Non-clinical Overview / Summary and Clinical Overview / Summary in Module 2,
- A declaration signed by the experts in Module 1.4.
- Brief information on the educational background, training and occupational experience of the experts in Module 1.4.

Experts should additionally indicate in their declarations the extent, if any of their professional or other involvement with the sponsor / dossier owner and confirm that the report has been prepared by them or if not, any assistance provided and by whom.

Reports should be based on an independent assessment of the dossier and references must be provided for any additional claims not supported by the dossier.

A sample declaration form is attached for this purpose.

'Local' (Australian) Experts

Sponsors are advised that a signed declaration is required for 'local' (Australian) experts, if used. The following is an example of a suitable declaration form:

Information about the Expert Quality /Non-clinical / Clinical (delete those not appropriate)

I, the undersigned, declare that I have:

- the suitable technical or professional qualifications to act in this capacity (for more information, refer to the enclosed *curriculum vitae*).
- fully examined the data provided by the applicant and have provided references to the literature to support statements made that are not supported by the applicant's original data. This report presents an objective assessment of the nature and extent of the data.
- provided a report based on my independent assessment of the data provided
- based my recommendations, regarding suitability for registration, on the data provided herewith. I have considered the attached data and have recommended as to suitability for registration of the intended dose forms and presentations according to the proposed product information document.

I further declare that this expert report represents my own view.

Further, I declare the following to be the full extent of the professional relationship between myself and the applicant:

.....
.....
.....
.....

QUALITY / NON-CLINICAL / CLINICAL (delete those not appropriate)

Name of the expert:

Signature:

Date:

Address:
.....
.....
.....

Overseas Experts

Sponsors should note that the TGA requires similar signed declarations from overseas experts, however, the following would also be acceptable:

Information about the Expert

Quality /Non-clinical / Clinical (delete those not appropriate)

According to his/her respective qualifications the undersigned expert declares hereby to have performed the duties set out in the Article 12.2 and in accordance with Annex I, Part I 1.4 of Directive 2001/83/EC, as amended.

QUALITY / NON-CLINICAL / CLINICAL (delete those not appropriate)

Name of the expert:

Signature:

Date:

Address:
.....
.....
.....

Module 1.5 Specific requirements for different types of applications

Documentation		
1	1.5.1	Literature base submission: Methodology of literature search, including complete details of any database search strategies
2		Declaration that the search strategy agreed with OPM prior to submission was followed OR Justification for the search methodology
3		Complete search output
4	1.5.2	Orphan drug: Copy of orphan drug designation
5	1.5.3	Genetically modified organisms: A copy of any written consents from the Office of the Gene Technology Regulator (OGTR)
6		
7	1.5.4	New product name: Declaration that Module 3 aspects of the new product are identical to the already registered product OR Information on differences and a declaration that other aspects are identical
8		Declaration that the PI and CMI of the new product are identical to the already registered product OR Information on differences and a declaration that other aspects are identical
9	1.5.5	Co-marketed medicine: Letter of access from the sponsor of the registered product
10		Declaration that quality (Module 3) aspects of the product are identical to the already registered product OR Information on differences and declaration that other aspects are identical
11		Declaration that the PI and CMI of the product are identical to the already registered product OR Information on differences and declaration that other aspects are identical

Module 1.5.1 Literature based submissions

If the normal supporting data set is not available, the TGA will consider accepting literature based submissions for the purposes of updating the Product Information documents of medicines with an extensive registration history, either in Australia or overseas. Under exceptional circumstances a literature based submission may be accepted for the registration of a new chemical entity, for example, a well characterised medicine marketed in other countries for many years.

For further information regarding literature based submissions, sponsors should refer to the *Literature Based Submissions: Points to Consider* document (2003)⁶.

Module 1.5.2 Orphan drug products

Orphan Drug Designation is available if specific criteria are met (see Sections 2.6.1 and

4.3.2 of the ARGPM). Interested sponsors should contact the relevant OPM Clinical Evaluation Section (see Appendix 4 of the ARGPM) for more information.

An application for the registration of a prescription medicine that has been granted Orphan Drug Status may be lodged without the payment of fees¹⁵.

Module 1.5.3 Genetically modified organisms

Genetically modified organism (GMO) means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

Sponsors intending to apply to the TGA to use a GMO as a medicine are advised to also consult the Office of the Gene Technology Regulator (OGTR) to determine their obligations under the *Gene Technology Act 2000*. Further information can be obtained from the OGTR website¹⁶.

In case of a medicine containing or consisting of GMOs the sponsor should include a copy of any written consent from the OGTR to the use of the genetically modified organisms.

Module 1.5.4 New product names

A sponsor may register an additional product name of its own, already registered medicine, in which case the application should include:

- An assurance that the ARTG record of the parent product is complete and accurate for all data fields¹⁷ (or that the TGA has been requested to correct the record) and **either** an assurance that all quality (Module 3) aspects of the new product are identical to the already registered product, except for labelling, **or** information on any differences together with an assurance that all other quality (Module 3) aspects are identical, and
- **Either** a statement that the PI and CMI are identical to those of the existing product, **or** a list of the differences.

Module 1.5.5 Co-marketed medicines

¹⁵ In exceptional circumstances the TGA may accept a concurrent application for orphan drug designation and registration. In these circumstances the sponsor would need to include an application for orphan drug designata ion and a justification for submitting concurrent applications for designation and registration in Module 1.13.2. The relevant evaluation fee would need to be paid, though this would be rebated in the event of a successful application for orphan drug designation.

¹⁶ <http://www.ogtr.gov.au>

¹⁷ If the record is not accurate, a formal request for the TGA to correct the record should be lodged before the application for the new product name is submitted.

A sponsor may authorise the TGA to use information on its already registered product for the benefit of another sponsor. In this case, the new product will be identical to the first product or at least very similar. This process is sometimes referred to as *cross licensing*. The application should normally include:

- A letter from the sponsor of the already registered product allowing the TGA to use information in the registration file on behalf of the applicant and stating whether or not the applicant may view the information on file. The letter should include an assurance that the ARTG record of the parent product is complete and accurate for all data fields¹⁸ (or that the TGA has been requested to correct the record).
- **Either** an assurance that all quality (Module 3) aspects of the product are identical to the already registered product except for labelling, **or** information on any differences together with an assurance that all other Module 3 aspects are identical.
- **Either** a statement that the PI and CMI are identical to those of the existing product, **or** a statement as to the differences.

¹⁸ If the record is not accurate, a formal request for the TGA to correct the record should be lodged before the application for the new product is submitted.

Module 1.6 *Drug and plasma master files and certificates of suitability of monographs of the European pharmacopoeia*

Documentation		
1.	1.6.1	Relevant <i>Drug and Plasma Master Files</i>
2.		Relevant <i>EDQM Certificates of Suitability</i>
3.	1.6.2	<i>Sponsor's Declaration</i>
4.	1.6.3	<i>Letters of Access to DMF</i> , as appropriate
5.		<i>Letters of Access to PMF</i> , as appropriate
6.		<i>Letters of Access to CEP</i> , as appropriate
7.	1.6.4	<i>Certificates of Suitability</i> (including any annexes), as appropriate

An application to register a new product (or vary an existing product) may make reference to a Drug Master File (DMF), Plasma Master File (PMF) or Certificate of Suitability of Monographs of the European Pharmacopoeia (CEP).

Where reference is made to a DMF/PMF, the finished product sponsor must have written permission to access the DMF/PMF from the company that supplied the DMF/PMF and must provide the DMF/PMF file number to the TGA.

Where reference is made to a CEP, the finished product sponsor must have written permission from the medicine manufacturer to access the CEP and must provide a copy of the CEP, and any appendices, to the TGA.

Procedures relating to DMF/PMFs and CEPs are outlined in more detail in Section 4.1.7 and Appendix 11 (*Drug Master Files and Certificates of Suitability*) of the ARGPM².

Sponsors should complete the proforma for *Relevant Drug and Plasma Master Files* and *Relevant EDQM Certificates of Suitability* (Module 1.6.1) and provide written assurance that there is a formal agreement between the active pharmaceutical ingredient manufacturer and the sponsor designed to ensure that information will be communicated by the manufacturer to the sponsor and the TGA before any significant change is made to the drug substance (Module 1.6.2).

Manufacturers should complete the *Proforma Letter of Access to DMF/PMF* or *Proforma Letter of Access to CEP*, as appropriate. These letters should be included in Module 1.6.3.

The sponsor's (*open*) part of the DMF should be included in Module 3.2.S of the Quality documentation presented in the CTD-format. The active substance manufacturer's restricted (*closed*) part is supplied to TGA directly by the active substance manufacturer.

Complete copies of the *Certificates of Suitability* (including any annexes) should be provided in Module 1.6.4 and Module 3 2.R.

Module 1.6.1 Relevant Drug and Plasma Master Files

Does the application make reference to a Drug Master File (DMF) or a Plasma Master File (PMF)?

NO

YES

If YES, identify **drug substance 1**:

Manufacturer's business name:

Full street address of manufacturing site:

Manufacturer's Client ID: *(if known)*

TGA DMF/PMF file number

Manufacturer's *letter of access* attached (*Module 1.6.3*)

NO

YES

Drug substance 2:

Manufacturer's business name:

Full street address of manufacturing site:

Manufacturer's Client ID: *(if known)*

TGA DMF/PMF file number

Manufacturer's *letter of access* attached (*Module 1.6.3*)

NO

YES

If the sponsor is unable to provide this information, the DMF/PMF cannot be accessed and the application cannot be accepted.

Please attach additional pages as required

Relevant EDQM Certificates of Suitability

Does the application make reference to a EDQM Certificate of Suitability (CEP)?

NO YES

If YES, identify **drug substance 1:**

Manufacturer's business name:

Full street address of manufacturing site:

Manufacturer's Client ID: *(if known)*

Certificate of Suitability number and version:

Manufacturer's *Letter of access* attached (*Module 1.6.3*)

NO YES

Drug substance 2:

Manufacturer's business name:

Full street address of manufacturing site:

Manufacturer's Client ID: *(if known)*

Certificate of Suitability number and version:

Manufacturer's *Letter of access* attached (*Module 1.6.3*)

NO YES

If the sponsor is unable to provide this information, the Certificate of Suitability cannot be accessed.

Please attach additional pages as required

Module 1.6.2 Sponsor's declaration

The following drug substances are the subject of a Drug/Plasma Master File:

The following drug substances are the subject of a EDQM Certificate of Suitability:

The drug substance(s) above is/are the subject of either a drug master file, a plasma master file or an EDQM Certificate of Suitability supplied with this application. Each drug substance manufacturer has been requested to forward to the TGA a letter of access authorising the TGA to refer to the DMF/PMF/CEP in its evaluation of this medicine. The letters of access (Module 1.6.3) include assurances regarding subsequent changes to the manufacture or quality control of the drug substance as required by the TGA.

A formal agreement exists between the sponsor of the medicine and each manufacturer of the drug substance(s) which ensures that information will be communicated between them and to the TGA before any significant change is made to the site of manufacture,

manufacturing procedure or quality control specifications of the drug substance. Except as permitted by the TGA's guidelines relating to changes to medicines, such changes will not be made to the drug substance(s) to be used in manufacture of medicines destined to be distributed in Australia before written approval is granted by the TGA. Both parties understand that the consequences of failure to obtain approval for changes where approval is necessary may include de-registration and recall of batches of medicines containing this material in Australia.

Signature: Date:

dd mm yy

Name:
(please print)

Position/ Relationship to Sponsor:

(Declaration must be signed by an authorised officer of the company)

Module 1.6.3 Proforma Letter of Access to DMF/PMF/CEP

Drug and Plasma Master Files

Head
Office of Prescription Medicines
Therapeutic Goods Administration
P O Box 100
Woden ACT 2606
Australia

Dear Madam

Authorisation to access Drug Master File¹⁹

Consent is hereby granted to the Therapeutic Goods Administration to make reference to this company's Drug Master File **{TGA file No:* }** for **{drug substance name}** in the evaluation of applications and notifications relating to the registration of **{medicine name(s)}** submitted to the TGA by the sponsor **{Australian sponsor's name}**.

This consent does/does not** include authorisation to supply information or extracts from or the whole of the data to:

{Name of company or individual}.

The substance is manufactured by:

{Names and addresses of all manufacturing sites and manufacturing steps carried out at site}

A copy of the *Sponsor's Part of the DMF* as specified in the European Community Drug Master File Procedure has been supplied to the sponsor.

A formal agreement exists between the sponsor of the medicine and the manufacturer of the drug substance which ensures that information will be communicated between them and to the TGA before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the drug substance. Except as permitted by the TGA's guidelines relating to changes to medicines, such changes will not be made to the drug substance to be used in manufacture of the medicine destined to be distributed in Australia before written approval is granted by the TGA.

I understand that the consequences of failure to obtain approval for changes where approval is necessary may include de-registration and recall of batches of medicines

¹⁹ This proforma may be used for either a DMF or a PMF. Please use the appropriate term.
CTD, Module 1, TGA, November 2008

containing this material in Australia.

This DMF (or data identical to that contained therein) has also been submitted to and approved by the regulatory authorities in **{list of countries with regulatory systems comparable to that in Australia}**, and the TGA is authorised to request and refer to the evaluation reports of these agencies. The TGA is also authorised to exchange its own evaluation reports with these and other overseas regulatory authorities.

Any questions arising from the TGA's evaluation of this DMF should be forwarded to:

{Name and address}

Yours faithfully

{Signature of Company Representative}

{Name}

{Position in Company}

{Date}

* Include TGA file reference if known, otherwise delete

**Delete as appropriate

Certificate of Suitability

Head
Office of Prescription Medicines
Therapeutic Goods Administration
P O Box 100
Woden ACT 2606
Australia

Dear Madam

Authorisation to access EDQM Certificate of Suitability

Consent is hereby granted to the Therapeutic Goods Administration to make reference to the Certificate of Suitability (CEP) No. **{Certificate number and version}** issued by the European Directorate for the Quality of Medicines (EDQM) on **{date of issue}** for this company's **{drug substance name}** in the evaluation of applications and notifications relating to the registration of **{medicine name(s)}** submitted to the TGA by the sponsor **{Australian sponsor's name}**.

The substance is manufactured by:

{Names and addresses of all manufacturing sites, and manufacturing steps carried out at site}

Assurance is given that any conditions or additional testing requirements attached to the Certificate by the EDQM will be complied with for any batch of the drug substance to be used in manufacture of medicines to be distributed in Australia.

A formal agreement exists between the sponsor of the medicine and the manufacturer of the drug substance which ensures that information will be communicated between them and to the TGA before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the drug substance. Except as permitted by the TGA's guidelines relating to changes to medicines, such changes will not be made to drug substance to be used in manufacture of medicines destined to be distributed in Australia before written approval is granted by the TGA.

Where relevant, any revised Certificates for this drug substance will be forwarded to the TGA for its information and records.

I understand that the consequences of failure to obtain approval for changes where approval is necessary may include de-registration and recall of batches of medicines containing this material in Australia.

This company also authorises the TGA to access the EDQM Evaluation Report Part A and/or B related to the issue of this CEP if the TGA considers this necessary.

Any questions arising from evaluation of this drug substance should be forwarded to:

{Name and address}

Yours faithfully

{Signature of Company Representative}

{Name}

{Position in Company}

{Date}

Module 1.7 Good manufacturing practice

Documentation		
1.	1.7.1	List of Australian manufacturers' names and licence numbers
2.	1.7.2	GMP clearance letters for all overseas manufacturing sites
3.	1.7.3	Copies of letters of application for GMP clearance for those overseas manufacturing sites without GMP clearance (not applicable for category 3 applications or self-assessment notifications).

For all medicines, irrespective of the country of origin, it is expected that key manufacturing and/or processing steps in the production of active ingredients and finished pharmaceutical products are performed in plants of acceptable standards (see Section 4.1.9 of the ARGPM²).

For Australian manufacturers, the sponsor should provide a list of manufacturer's names and licence numbers.

The TGA's *Guidelines on the GMP clearance of overseas medicine manufacturers*²⁰ provides detailed information on how to obtain GMP clearance for overseas manufacturers. GMP certificates or equivalent evidence of GMP should not be submitted to the OPM along with Category 1, 2 or 3 applications or self-assessment notifications. Instead, such documentation should be submitted to the TGA's Office of Manufacturing Quality (OMQ) along with an application for GMP clearance.

To apply for a GMP clearance of an overseas manufacturer, sponsors must complete an electronic Clearance Application via the TGA eBusiness Services²¹

Category 1 applications for new medicines

Any Category 1 application submitted to the OPM for the new registration of a medicine in which overseas manufacturing sites are involved should, where possible, be accompanied by current and relevant GMP clearance letters issued by the OMQ of the TGA. Clearances should be valid for at least 6 months, and preferably 24 months, at the time of application.

If clearances have not been issued at the time of submission of the application, the application may be submitted and copies of the clearances forwarded to OPM as soon as they become available.

If GMP clearance is due to expire during the evaluation process, the sponsor must ensure GMP clearance letters are current at the time of registration.

²⁰ <http://www.tga.gov.au/manuf/gmpsom.htm>

²¹ <https://www.ebs.tga.gov.au/>

Final approval of the application cannot be granted until the GMP clearances are submitted.

Category 3 applications and self-assessment notifications

Any Category 3 application for approval of a change involving overseas manufactures or any self-assessment notification (SAN) of such a change must be accompanied by a current and relevant GMP clearance letter issued by the OMQ, in addition to any other supporting data required for the change. Where a GMP clearance is required but has not been provided at the time of submission, the application or notification cannot be accepted for processing. Merely providing evidence or an assurance that relevant GMP certificates have been submitted to OMQ for the issue of a GMP clearance letter is not acceptable for this purpose.

Company name change with no change in site address

GMP clearance may also be required when an overseas manufacturer changes its company name. Acceptable evidence of GMP, together with the new company name should be submitted to the OMQ. Any GMP clearance letter issued by the OMQ, together with a covering letter from the sponsor, should then be forwarded to the Information Technology Section, Business Management Group of the TGA with a request to update the client database. This will ensure that ARTG entries for the products concerned include the new company name.

Module 1.8 Meetings

Documentation		
1.	1.8.1	Details of compliance with meeting outcomes (Scientific Advice)
2.	1.8.2	Details of compliance with meeting outcomes (Pre-submission meeting)
3.	1.8.3	Details of any additional data to be submitted

The sponsor should also include details of compliance with the recommendations of any meetings held with the TGA and concerning technical aspects of the development of the medicine (Scientific Advice) or the submission (Pre-submission meeting) (see Section 3.1.1 of the ARGPM²).

If the TGA has agreed to accept additional data during the course of evaluation (see Section 3.1.3 of the ARGPM), details should be included in Module 1.8.

Module 1.9 *Individual patient data*

Documentation		
1.	1.9	Declaration concerning the availability of individual patient data

Data in respect of each individual patient from each clinical trial are not required to be included in the documentation at the time of application, except in the case of any bioavailability studies where individual patient data (IPD) for plasma concentrations and derived data are required.

Individual patient data may be included in the documentation if the sponsor considers it appropriate. Note: Individual Case Report Forms are not accepted as individual patient data.

Before an application is submitted, sponsors should ensure that individual patient data are readily available in the format that would be acceptable for submission in the EU or the USA. In general this is tabulated patient data that includes clinical and laboratory monitoring results, presented in such a way as to enable a relation to individual patients. A statement that these data can be provided must be supplied, identifying if necessary any studies for which individual patient data are not available. This statement should be included in Module 1.9.

The individual patient data, if not already supplied, may be requested during the evaluation period and, if a request for these data is not met within 15 working days, the application will usually lapse. Individual patient data may be requested by the TGA:

- to support a particular study if, during the evaluation, there is any reason to doubt the analysis or conclusions reached;
- if, after registration, the application is selected for auditing of the summary results and conclusions. Selection for auditing will be on a random basis, unless an overseas rejection is being investigated, and could involve approximately 10% of applications.

If a marketing application for the medicine has been rejected in the USA or Canada before or during the Australian evaluation process, for reasons related to the clinical data in any way, full individual patient data must always be available and may be required to be submitted in Australia. In the event that the Australian evaluation process has commenced, applicants should contact the Director of the relevant Clinical Evaluation Section to discuss.

Module 1.10 Overseas regulatory status

Documentation		
1.	1.10.1.	List of countries in which a similar application has been submitted
2.	1.10.2	Product Information from Canada, the Netherlands, New Zealand, Sweden, UK and USA
3.	1.10.3	Differences in the data set in applications submitted in Australia, Canada, the Netherlands, New Zealand, Sweden, UK and USA
4.	1.10.4	Regulatory status in Canada and USA

Sponsors are advised that this module should be completed for all applications (including those for generic products.)

They should also note that an updated overseas status report is required at the time of ADEC consideration (or the time at which the TGA Delegate decides on approval if not referred to ADEC).

Module 1.10.1 List of countries in which a similar application has been submitted

The sponsor should provide, in Module 1.10.1 of the dossier, a list of countries in which a similar application has been submitted, dates of submission (if available) and the status of these applications. This should detail approvals (with indications) and deferrals, withdrawals and rejections with reasons in each case. Where applications have been submitted to agencies in the European Union, the sponsor should also identify the type of application (centralised, mutual recognition or national). For centralised applications, the rapporteur and co-rapporteur should be identified and for mutual recognition applications, the reference member state should be identified.

Module 1.10.2 Overseas product information

In the case of marketing authorisations in Canada, the Netherlands, New Zealand, Sweden, UK and USA, copies of the Canadian Product Monograph, the Summary of Product Characteristics (SPC) in the Netherlands, Sweden and UK, Data Sheet in New Zealand and Prescribing Information (PI) in USA, should be supplied in Module 1.10.2. If the overseas SPC, monograph or PI has not been approved at the time the application is lodged in Australia, a draft document may be included. The approved overseas SPC, monograph or PI should then be supplied to the TGA as they become available.

Module 1.10.3 Data set similarities

Module 1.10.3 should contain a summary of the similarities / differences in the data packages submitted in Canada, the Netherlands, New Zealand, Sweden, UK and USA.

Module 1.10.4 Statement on whether an application for the product has been rejected, withdrawn or repeatedly deferred in the USA or Canada

Sponsors must declare whether a marketing application for the medicine has been rejected in the USA or Canada prior to lodgement of the application in Australia. If the medicine has been rejected, repeatedly deferred or withdrawn in Canada or withdrawn or denied approval in the USA, then full individual patient data must be submitted (see also Module 1.9). If rejection in the USA or Canada occurs during the Australian evaluation process, the TGA should be informed.

Module 1.11 Summary of biopharmaceutical studies

Documentation		
1.	1.11	<i>Summary of a Bioavailability or Bioequivalence Study</i> OR Justification for not providing biopharmaceutical studies, including references

Australia's requirements for biopharmaceutical studies are aligned with the CHMP *Note for Guidance of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98)²² which has been formally adopted in Australia (with amendment).

In relation to the content of biopharmaceutical study reports, this guideline states that:

The report of a bioavailability or bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with GCP-rules and related EU and ICH E3 guidelines. This implies that the authenticity of the whole report is attested by the signature of the principal investigator. The responsible investigator(s), if any should sign for their respective sections of the report.

The TGA considers it essential that the principal investigator(s) sign the study reports after their completion, either in an unqualified fashion or clearly taking responsibility for all aspects of the conduct of the study for which they might reasonably be held responsible. If the signature of the principal investigator is absent from the report of a bioavailability or bioequivalence study, it will be sought by the TGA during the evaluation process via a Section 31 request.

In addition to the requirements outlined in the CHMP *Note for Guidance on Investigation of Bioavailability and Bioequivalence*, the OPM also encourages applicants to complete the optional *Summary of a Bioavailability or Bioequivalence Study*²³ and include the completed summary form in Module 1.11. The summary form is designed to assist the OPM in examining the relevance and adequacy of biopharmaceutical data prior to acceptance of an application.

If an applicant wishes to justify not providing a biopharmaceutical study, Appendix 15 of the ARGPM provides a minimum set of issues to be addressed in any justification.

If a sponsor has justified why biopharmaceutical data has not been submitted (in accordance with the ARGPM requirements), then Module 1.11 should also contain the references for the justification.

²² <http://www.tga.gov.au/docs/pdf/euguide/ewp/140198entga.pdf>

²³ <http://www.tga.gov.au/docs/html/forms/pmbiosum.htm>

Module 1.12 Paediatric development program

Documentation		
1.	1.12	References to paediatric development program

There is a recognised global problem with the availability of paediatric-specific formulations and a lack of information from proper investigations of the use of medicines in children. This problem leads to medicines being used outside of their approved indications, and, at times, being reformulated by pharmacists to make them more suitable for use by children. However, the basic precept that children should not be discriminated against by being supplied poorly investigated medicines has been accepted internationally.

The TGA has adopted internationally recognised ICH/European guidelines dealing with paediatric data generation and facilitating the extrapolation of data from one patient population to another. The CTD guidelines require that the safety and efficacy in the paediatric population should be routinely analysed in applications for a proposed indication that occurs in children. These guidelines can be found on the TGA website.

Please state whether there is a paediatric development program for this medicine and if so, the relevant sections of the dossier.

Module 1.13 Information relating to Pharmacovigilance

Documentation		
1.	1.13.1	<i>Risk Management Plan</i>

1.13.1 Risk Management Plan for Australia

A detailed description of a risk management system should be provided, where appropriate, in the form of a Risk Management Plan (RMP), as outlined in Chapter 1.3 of *EudraLex Volume 9A – Pharmacovigilance for Medicinal Products for Human Use* (version September 2008).

The RMP contains 2 parts:

- Part I of the RMP incorporates the Safety Specification and the Pharmacovigilance Plan;
- In Part II, on the basis of the Safety Specification, the sponsor should consider carefully the need for risk minimisation activities to be introduced. Risk minimisation activities may be “routine” or “additional”. Within the “evaluation of the need for risk minimisation activities,” the sponsor should discuss fully the use of routine risk minimisation activities and whether there is a need for additional risk minimisation activities. If only routine risk minimisation activities are required there is no need to submit a risk minimisation plan. If additional risk minimisation activities are thought necessary, the sponsor should provide a risk minimisation plan within Part II of the RMP. This risk minimisation plan should contain both the routine and additional activities for each safety concern.

A RMP may need to be submitted at any time of a product’s life-cycle, i.e. during both the pre-registration and post-registration phases. In particular, a RMP should be submitted:

- with the application for the registration of:
 - any product containing a new chemical entity;
 - a similar biological medicinal product; or
 - a generic medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product;
- with an application involving a significant new registration (for example, new dosage form, new route of administration, significant change in indications) or a significant change in a registration (for example, new manufacturing process of a biotechnologically-derived product) unless it has been agreed with the TGA that submission is not required;
- on request from TGA (both pre-and post- authorisation); or

- on the initiative of a sponsor when they identify a safety concern with a medicinal product at any stage of its life cycle.

In some circumstances, products which are not in the above categories which are seeking a new registration may require a RMP:

- known active substances
- literature based submissions
- fixed combination applications.

It is strongly recommended that discussions with the TGA on the need for, and content of, a RMP should take place in advance of submission, especially for situations where the submission of a RMP is not mandatory.

The RMP should be presented in a stand-alone format (separate volumes in paper) allowing circulation to, and evaluation by pharmacovigilance and risk management experts. It should be accompanied by other relevant documents such as study protocols, where applicable.

Annex I Environmental risk for non-GMOs (genetically modified organisms) containing medicines

The documentation for the environmental risk assessment should always be bound in a separate volume.

Applications to register prescription medicines for human use should include in Annex 1 an indication of any potential risks presented by the medicine for the environment. This requirement is particularly applicable to new active substances and live vaccines.

Applications for new active substances may include in the documentation provided, an indication of relevant environmental hazards, making reference to standard physicochemical tests and any appropriate testing they have conducted on biodegradability, including some testing in sensitive species.

Applications for live vaccines should consider issues such as shedding, survival and capacity to disseminate.

The risk assessment overview should include an evaluation of possible risks to the environment from the point of view of use and/or disposal and make proposals for labelling provisions that would reduce this risk.

Annex II Antibiotic resistance data

In response to the *Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) Report* (released in October 1999) and *The Commonwealth Government Response to the Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR)*, the TGA anticipates that antibiotic resistance data will need to be submitted here in the future.

Please contact the Director, Clinical Evaluation Section 2, for more information.

Annex III Overseas evaluation reports

For a Category 2 application, two independent evaluation reports from *acceptable countries*, where the product is already approved, are required to be provided at the time of application. Currently the countries identified by the Minister as *acceptable*, for the purposes of providing evaluation reports, are Canada, Sweden, the Netherlands, the United Kingdom and the United States of America. For further details about Category 2 applications see Sections 2.5.2, 3.5.1 and 4.2 of the ARGPM. Copies of these evaluation reports should be provided as Appendix III to Module 1.