Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Medical Device Requirements Version 4

under the Therapeutic Goods Act 1989

May 1998
Volume 1 of 2

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

2.0 REGISTRABLE DEVICES

2.1 INFORMATION APPLICABLE TO ALL REGISTRABLE THERAPEUTIC DEVICES

The *Therapeutic Goods Regulations* state that for the purposes of evaluation a sponsor of a Therapeutic Device must 'satisfactorily establish the quality, safety and efficacy' of the device.

In undertaking the evaluation, the Conformity Assessment Branch will assess the data provided to **confirm** that the device should operate in a safe and reliable way and that the specifications have been correctly implemented. This is achieved primarily through examining the manufacturer's own tests and through performing some in-house testing. Design, material assessment and selection, testing protocols, etc. will be reviewed to ensure results are consistent with the claimed specifications.

This review may include assessing conformance to standards, testing protocols and results, GMP and other regulatory requirements. If, after assessment, the device is judged unsafe or unreliable, or if its operation is not properly specified in general, the TGA will reject the application for general marketing. However, the sponsor may be able to change the device or literature to address the CAB's concerns while not undermining the studies that have been conducted for the product.

In most cases, clinical or preclinical studies will be required to determine that the device specifications adequately match the operational requirements or clinical usage of the device.

There are several categories of evaluation detailed in Item 6 of Schedule 9 of the *Regulations*, under which evaluation fees may be charged.

Evaluation Fee Structure

Design / Materials / Testing

This evaluation category is applicable when:

- the device's functional specifications and design; and/or
- the physical properties of the materials used in the construction of the device; and/or
- labelling, packaging, instructions, patient information, Promotional Material and service manuals; and/or
- the testing of the performance of the device against its specifications undertaken by the manufacturer,

require evaluation.

Manufacture/Quality Control/Sterility

This evaluation category is applicable when:

- the manufacturing process for the device; and/or
- the quality assurance/control system used to assess the conformity of the device with its specifications; and/or
- the sterilization assurance process for the device,

require evaluation.

Assessment of quality assurance/control systems is carried out by the GMP and Licensing Section (GMPALS) of Conformity Assessment Branch. The evaluation of the sterilization processes is carried out by the Microbiology Section, Therapeutic Goods Administration Laboratories Branch (TGAL).

Biocompatibility/Preclinical

This evaluation category is applicable when:

- the interaction between the device and body tissues or fluids; and/or
- the performance of the device assessed by animal in vivo testing prior to the clinical use of the device,

require evaluation.

Human Clinical Data

Evaluation of data in this category is required when the performance of the device is assessed from the results of clinical trials undertaken by the sponsor or manufacturer of the device.

Low Level Evaluation Fee

Low level registrable devices incur a flat evaluation fee. Refer to Appendix 9*Fees and Charges.*

Format of Registrable Device Submissions

Each submission must comply with the information specified in this chapter, as well as with any additional information requested in the relevant individual registrable device chapters. To assist the sponsor to compile submissions, a checklist is given in Table 2.1, and a similar checklist has been included in each registrable device chapter. The checklist summarises all the information required by the TGA for a registrable device, and gives an indication of the evaluation fees which could be incurred.

General Details

Each registrable device submission must include the items listed here:

- dated application letter clearly expressing the purpose of the application, including
  - sponsor details: name, address, phone and fax number, contact name, email address and TGA Enterprise ID number (if available);
- *Enterprise Details* form (if applicable);
- *Therapeutic Devices Application* form;
- application fee;
- table of contents including indexing appendices and attachments;
- proprietary name of the device/s;
- mark and/or model number for each device;

- a brief description of the device, including photographs and/or drawings (not facsimile copies), videos or software demonstration packages;
- technical and clinical specifications for the device;
- any other media or material which could assist in the evaluation of the device.

Risk Analysis

Refer to Chapter 2.5 *Risk Analysis.*

Table of Equivalence

A table of equivalence is required to demonstrate the similarities and differences between a *predicate* device and the submitted device.

If equivalence is not being claimed, this should be clearly stated in the submission.

Commercial History, Regulatory Actions and Regulatory Status

New Device

Provide a brief description of the development of the device including:

- date of first implant,
- marketing in each country other than Australia,
- details of the regulatory status (marketing approval) obtained in each country,
- a summary of device-related incidents reported to the manufacturer since the introduction of the device in the market. If no problems have been reported then a statement to that effect must be included.
- details of any regulatory action relating to the device in any country, including certificates or notifications where appropriate, e.g. rejection of marketing approval, recall, hazard alert, explants and modifications made following an action.

Predicate Device

If a predicate device has been approved for supply in Australia, against which equivalence is being claimed, the following information must be supplied for the predicate device:

- a brief description of the development of the device,
- date of first implant/marketing in each country including Australia,
- number of devices implanted in each country,
- details of the regulatory status (marketing approval) obtained in each country,
- a summary of device-related incidents reported to the manufacturer since the introduction of the device in the market. If no problems have been reported then a statement to that effect is necessary.
- details of any regulatory action relating to the device in any country, including certificates or notifications where appropriate, e.g. rejection of marketing approval, recall, hazard alert, explants and modifications made following an action.

Refer also to Chapter 2.3 *Equivalence / Abridged Submissions*.

Good Manufacturing Practice (GMP)

The sponsor must supply evidence that the principal manufacturer and alternative manufacturers and any subassemblies provided by third party manufacturers comply with an acceptable code of GMP. Information provided must also include:

- manufacturer name and exact address of the site,
- any registration number granted by the local authorities,
- TGA Enterprise ID number (if available).

Refer also to Chapter 1.19 *Good Manufacturing Practice.*

Reporting Conditions

A number of standard conditions apply to all therapeutic goods entered in the ARTG. In some instances, additional conditions may apply for some specific device groups. Reports of problems with Registrable devices must be supplied annually for three years after approval for entry in the ARTG. Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance

Refer to Chapter 1.6 *Postmarket Compliance Programs.*

Samples

TGA may request the provision of a sample of the device for examination. Samples should be supplied in the original packaging and included with the submission data.

Disclaimer — Submitted Samples
Any goods requiring special care must be accurately described by the sponsor and any necessary special precautions stated on or before submission of the goods. If this is not done TGA shall be under no liability for their deterioration, loss, damage or destruction from any cause whatever including negligence on the part of the TGA or its employees. The TGA shall not be liable for any damage to or destruction of the goods resulting from evaluation tests conducted in relation to the goods except such as shall arise from its negligence.

Quarantine

Under the *Quarantine Act (1908)*, sponsors are required to obtain approval from the Australian Quarantine and Inspection Service (AQIS) to import products of biological origin. Refer to Chapter 1.4 *Quarantine Requirements.*

Design / Materials / Testing

Design and Construction

The sponsor shall submit a description of the device including:

- purpose of the device and its intended use;
- indications and contraindications for use;
- good quality photographs and product drawings showing device construction, e.g. control panels, open and closed doors or lids, connections, dimensions of the assembled device, components and accessories;
- for electrical or electronic devices, detailed block or functional diagrams (circuit diagrams may be requested if necessary);
- details of the energy source, means of recharging or replacing the energy source;
- description and general block diagram of any internal software;
- a list of all performance characteristics and device specifications;
- details of any specific disposal requirements.

Construction

The sponsor shall submit:

- good quality copies of mechanical drawings showing the assembly of the complete device;
- details on formulations or treatments of, or to, the constituent materials of the device.

Materials

The submission should include a description of the device, its specifications and the source of each material from which the device is constructed. For device materials which are critical to the safety and effectiveness of the device (e.g. seals preventing ingress of fluids, electrical contacts on which functionality depends, tissue contacting materials, etc.) details of the material properties which support its use must be provided.

Labelling

Labels (draft or sample) complying with the current labelling order must be provided.

Packaging

A detailed description of the packaging and its ability to preserve the integrity and, if applicable, the sterility of the device, must be provided.

Product Information / Instructions for use / Promotional material

All product literature (copies or actual) provided with, or used in the marketing of, the device must be provided. This includes, but is not limited to:

- User Manuals, Programming Manuals, Programming Instructions or equivalents;
- Physician Manuals and Implanting Instructions;
- Technical Manuals or similar, including specifications;
- copies of any information provided separately to clinical staff, including training or instructional literature, video cassettes, movies or visual aid materials;
- copies of any information provided separately to patients including warnings and cautions;
- copies of any promotional or advertising material concerning the device, components and accessories;
- forms and details of any systems used to track and trace the device.

Testing

The sponsor shall submit:

- details of any and all testing programs other than in vivo and clinical trials

Sponsors are responsible for ensuring that any Product Information supplied separately from the product, for whatever purpose, is entirely consistent with the information supplied with the product and approved during evaluation, and that additional claims are not made without prior approval.

Manufacturing / Quality Control / Sterility

Manufacturing Process

Full details of each major step in the manufacturing process, including a flow chart, shall be provided. If manufacture is carried out at different sites, this should be indicated on the flow chart, including the details of control exercised over the transferred subassemblies.

Quality Control

Details of the procedures and processes used by the manufacturer to ensure that critical product specifications are met during routine production must be provided.

Sterility

Details on the sterilization process for the device must be provided. Refer to Chapter 2.6 *Sterility*.

Biocompatibility / Preclinical

Biological Safety and Biocompatibility Testing

Refer to Chapter 2.7 *Biological Safety and Biocompatibility Testing.*

Preclinical Studies

Details of any in vivo testing performed prior to the clinical trial of the device must be provided.

Human Clinical Data

Refer to Chapter 2.8 *Human Clinical Data.*

Submission Content Style

Language

All information must be submitted in English. Where material is not originally in English an authenticated translation should be submitted. TGA reserves the right to request the original material at any time.

Units

Metric units shall be used. Units generally accepted in clinical practice may also be used, e.g. mmHg.

Text, Drawings, Photographs and Videos

All text and drawings must be legible and drawings clearly labelled. Drawings must be full size copies but not facsimile reproductions. Photographs must be originals (not photocopies), and must be clearly labelled with references to the submission, unless bound into submissions. Any videos must be clearly labelled with references to the submission.

Written Information

All written material, apart from drawings, brochures and manuals, should be submitted on A4 size paper, on 3.5" computer disks in WordPerfect or Word format, or on a compact disk in PDF format. The written material should be bound in loose leaf binders and the spines should be such that the folder will open flat. The thickness of each binder/folder should not exceed 30 mm and external dimensions must not exceed 255 x 370 mm.

Division of Data into Volumes

The information requested for Clinical Studies (Chapter 2.8) should be presented as a separate volume(s) or disk and should include a copy of the information specified under the subsection titled *General Details* earlier in this chapter.

Number of Copies

The original and one complete copy of written material must be submitted. Other copies may be requested if required. Two copies of any computer disk must be submitted.

Presentation

Each volume should be clearly labelled on the spine and the front cover with:

- device name,
- sponsor name,
- DR4 chapter name, volume and copy numbers,
- DR4 checklist for the relevant chapter.

Computer disks must be clearly labelled with the name of the sponsor and the submission title.

Pagination

All pages must be serially numbered throughout the submission. In correspondence, all references should specify not only the page numbers but also the volume of the submission.

Indexing, Cross-referencing, and Labelling

A table of contents should be included at the front of the first volume and sub-tables at the front of each subsequent volume. The table of contents should refer to the chapters and headings used in DR4 and follow the same order. Submissions should include in the main text any references to addenda and technical drawings.

Submissions Formatted for Other Regulatory Authorities

Submissions formatted according to the requirement of DR4 are preferred. Submissions prepared for other regulatory authorities may be accepted if:

- the information is fully cross-referenced to the requirements of DR4; and
- all the information required by DR4 is supplied.

Table 2.1. Application Checklist

SAMPLE ONLY

A tick ✓ indicates information that is to be supplied as part of the submission

Contents of registrable device submissions	General Information Requirements	Additional Information Required
General Details	✓	*
Risk Analysis	✓	*
Table of Equivalence #	✓	*
Commercial and Regulatory History	✓	*
GMP	✓	*
Reporting Conditions	✓	*
Post Market Surveillance	✓	*
Photographs, videos, drawings or samples (if required)	✓	*
Quarantine ##	✓	*
		*

Fee Structure	Evaluation Categories (refer page 52)	General Information Requirements	Additional Information Required
Design /	Design / Construction	*	*
Materials /	Materials	*	*
	Labelling	*	*
	Packaging	*	*
	Construction	*	*
	PI/ Instructions for Use /PM **	*	*
Testing (Refer page 55)	Testing	*	*
Manufacturing / Quality Control / Sterility (Refer page 56)	Manufacturing	*	*
	Quality Control	*	*
	Sterility	*	*
Biocompatibility /	Biological Safety / Biocompatibility Testing	*	*
Preclinical (Refer page 57)	Preclinical	*	*
Human Clinical Data (Refer page 57)	Human Clinical Data	*	*

\# to be included if equivalence is being claimed

should comply with AQIS requirements for imported devices containing human or animal-derived material

* information required as specified in individual registrable device chapters

** Product Insert / Instructions for Use / Promotional Material

2.2 GROUPING OF REGISTRABLE DEVICES

Therapeutic Goods (Single Therapeutic Goods) Order No.1 of 1991 (Appendix 19) provides for grouping of separate and distinct registrable devices if they:

- have the same sponsor; and
- have the same manufacturer; and
- are classified in the same Australian Device Group (ADG); and
- if the devices are PMMA (polymethyl-methacrylate) posterior chamber intraocular lenses (IOL), have the same composition and do not differ by more than the specified design parameters in relation to the parent lens; and
- if the devices are implantable cardiac pacing system leads, including leads for pulse generators, defibrillators, cardioverters and anti-tachycardia devices that differ only in the length of the leads; and
- if the devices are heart valves, differing only in the size of the valves; and
- if the devices are of human or animal origin that differ only in size; and
- are accessories to a powered drug infusion device.

This Order is available from Government Info Shops in each capital city. Refer to Appendix 13, *Therapeutic Goods Orders and Standards* for address details. It is proposed that the grouping provisions included in the Order will be extended to include disinfectants, breast implants, cardiovascular grafts, cardiac pacers and pulse generators and to extend the grouping criteria for devices of human and animal origin and implantable cardiac pacing leads.

Appendix 6 contains a summary of ECRI codes cross referenced to Australian Device Groups (ADGs).
The complete edition of Australian Device Groups (ADGs) and ECRI code information is contained in The*Australian Device Groups* document available from the

TGA Publications Office
ph: 1 800 020 653
fax: 02 6232 8605
web site: http://www.health.gov.au/tga
email: tga-information-officer@health.gov.au

Enquiries concerning the status of lodged Registrable device applications should be directed to the Medical Devices Section:
ph: 02 6232 8777
fax: 02 6232 8687

2.3 EQUIVALENCE / ABRIDGED SUBMISSIONS FOR REGISTERED DEVICES

Sponsors and/or manufacturers who wish to claim that the registrable device to be entered in the ARTG is equivalent to a predicate device which has been approved for supply in Australia, may be able to lodge an abridged submission to support their application. Objective evidence that satisfactorily establishes the quality, safety and efficacy of the goods for the purposes for which they are to be used may be sourced from three areas:

- the evaluation of submitted new data;
- the sponsor providing evidence that a device submission is equal in intended use, manufacturing processes and technological characteristics to a previously evaluated and registered device; or
- the justification of the equivalence of specifications/materials/processes, to a previously evaluated and registered device, if small variations exist.

The claim for equality and/or equivalence will be assessed on receipt of the application for entry in the ARTG. Where the claims cannot be substantiated, the application will be rejected with the loss of the application fee. Where the claims for equivalence are accepted, the Director of Conformity Assessment Branch has the delegation from the Minister to waive or reduce the evaluation fees.

Sponsors who are not manufacturers

Sponsors who are not manufacturers must confirm that:

- a copy of the equivalence application been provided to the device manufacturer;
- the device manufacturer has confirmed receipt and understanding of that document;
- a clear statement has been received from the manufacturer confirming their belief that the specified characteristics of the sponsored device are equivalent to those of a nominated registered device;
- the manufacturer has formally advised the sponsor of all modifications to the device's intended functions, manufacturing process and technological characteristics;

and must specify that:

- any changes or modification to the device's intended use, critical to its safety and efficacy, have been made; or
- any changes or modification to the device's manufacturing processes, critical to its safety and efficacy, have been made; or
- any changes or modifications to the device's technological characteristics, critical to its safety and efficacy, have been made.

Regardless of whether or not a claim of equivalence is submitted, all data supporting any changes to therapeutic devices should be documented and held on file by the manufacturer for GMP audit purposes and for approval in certain instances.

Modification of a Registered Device or a New Device

Where Intended Use, Manufacturing Processes and Technological Characteristics vary slightly from a predicate device and the sponsor believes that the effect of the change is negligible, then a substantiated claim for *equivalence* may be made. This evidence should be submitted as a *Table of Equivalence* in which the differences are highlighted, and as a statement explaining why the sponsor believes that the differences are inconsequential to the quality, safety and efficacy of the submitted device.

In most cases, only **new** data supporting changes to the quality, safety and efficacy of the whole of the submitted device will be evaluated.

Changes in the intended use, manufacturing process or technological characteristics of a registered device or its components, must be validated against the manufacturer's specifications. The manufacturer must be able to demonstrate, through standard validation techniques, that these changes will have no detrimental effect on the safety and efficacy of the device. In the absence of this validation, a submission describing the changes must be accompanied by additional data for evaluation.

A product Master File is helpful when providing data to establish that variations to the initial device do not affect its safety and efficacy. A product Master File can describe the specifications, materials and manufacturing processes which are common to the initial model and subsequent variations of the device. For example, elements of a Master File may address aspects such as validation of sterilization procedures, body-contacting biomaterials and manufacturing processes.

Evidence of equality will not require justification other than a reference to Master File page numbers or a detailed description, but may be subject to investigation during TGA audits. Equal data will not require evaluation and will minimise evaluation time and evaluation fees. In the absence of a Master File a clear and detailed description of the aspects of the current and predicate devices that are identical in every way must be provided in each submission.

Equivalence cannot be claimed for changes to products described in Appendix 3, *Changes to Therapeutic Devices*, where approval or notification is required from TGA.

2.4 OVERSEAS EVALUATIONS

As part of the review of submissions for entry in the ARTG, evaluation reports prepared by overseas regulatory authorities will be consulted whenever possible. There are three main ways in which this approach can be used by the TGA. Sponsors can select any of these approaches which is appropriate to the Australian classification and to their therapeutic device.

Approvals from Overseas Regulatory Agencies which form part of the TGA evaluation process

US FDA Approvals

Where a product has been evaluated overseas, the regulatory authorities may, subject to the permission of the sponsor and manufacturer of the product, release a copy of the evaluation report to the TGA.

The majority of the devices referred to in DR4 are subject to premarket assessment, by the FDA for example, and an agreement has been reached which will allow exchange of information with the TGA. Application for registration in Australia will imply the TGA has the sponsor's permission to liaise with the FDA's Centre for Devices and Radiological Health whenever this is necessary.

The submission to the TGA should include copies of official FDA documentation certifying that the approval has been granted. Whilst FDA approval will generally be sufficient for listable devices and a PMA (Pre Market Approval) certificate for registrable devices, a 510k approval may not be sufficient for registrable devices.

EU Approval (CE mark) — Registrable Device Applications

Where an evaluation has previously been completed within the European Community, the Australian sponsor may like that evaluation to be taken into account in assessing the level of evaluation required in Australia. If so, the application for entry in the ARTG should include a letter, directed to each relevant notified body, giving consent, from the sponsor and the European supplier or manufacturer who submitted the original submission to the Notified Body, for the release of the relevant evaluation report to the TGA.

There are five conformity assessment routes that may be taken for Active Implantable Medical Devices (AIMDs), Class III and Class IIb medical devices falling in the registrable category, and the types of certification provided by EU Notified Bodies are different for each of these. The following covers the routes taken by the majority of CE marked medical devices. The Annex 4 route to CE marking is used infrequently, and as it does not include quality systems certification it cannot be used for registrable devices in Australia. Similarly, Annex 6, used for Class IIb devices, is not included as it is used infrequently and provides for EN 46003 certification.

AIMDs/Class III devices (most registrable devices)

- manufacturer's EC declaration of conformity; and
- either
  - EN 46001 Quality Systems certificate (Annex 2) and EC Design Examination certificate (Annex 2); or
  - EC Type Examination certificate (Annex 3) and EN 46002 Quality Systems certificate (Annex 5).

Class IIb devices (IOLs, breast implants)

- manufacturer's EC declaration of conformity; and
- either
  - EN 46001 Quality Systems certificate (Annex 2); or
  - EC Type Examination Quality Systems certificate (Annex 3) and EN 46002 certificate (Annex 5).

Specific enquiries relating to Notified Body certification should be directed to

Medical Devices Section
Conformity Assessment Branch, TGA

ph: 02 6232 8704
fax: 02 6232 8687

EU Approval (CE mark) — Listable Device Applications

The following conformity routes for listable therapeutic devices which are CE marked are acceptable to the TGA. Provided that copies of all the certification referred to below are provided with a submission to the TGA, the TGA undertakes no further review of the submissions for entry in the ARTG for these devices.

Class IIb

- manufacturer's EC declaration of conformity; and
- either
  - EN 46001 Quality Systems certificate (Annex 2); or
  - EC Type Examination certificate (Annex 3) and EN 46002 Quality Systems certificate (Annex 5);
  - EC Type Examination certificate (Annex 3) and product verification by Notified Body (Annex 4);
  - EC Type Examination certificate (Annex 3) and EN 46003 Quality Systems certification.

Class IIa devices need:

- either
  - manufacturer's EC declaration of conformity(Annex 7) and EN 46001 Quality Systems certificate (Annex 2); or
  - manufacturer's EC declaration of conformity (Annex 7, includes self certification of design) and EN 46002 Quality Systems certificate; or
  - manufacturer's EC declaration of confomity (Annex 7, includes self certification of design) and EN 46003 Quality Systems certificate; or
  - manufacturer's EC declaration of conformity (Annex 7, includes self certification of design) and product verification by notified body (Annex 4).

Class I Non-sterile, Non-measuring Function

- manufacturer's declaration of conformity (Annex 7— self certification of design and production); and
- class I register information— identity of Competent Authority to whom device(s) notified.

Class I Sterile, Measuring Function

- manufacturer's declaration of conformity (Annex 7— self certification) and EN46002 Quality Systems certification of sterilization/measuring features; or
- manufacturer's declaration of conformity (Annex 7— self certification) and verification of notified body of measuring features (Annex 4); and
- class I register information— identity of Competent Authority to whom device(s) notified.

Approvals from Overseas Regulatory Agencies which can be used to abridge the evaluation process for a registrable device

The Therapeutic Devices Evaluation Committee (TDEC) has endorsed 'Five Point Acceptance Criteria' which will be used to abridge the review of registrable medical devices by the TGA. The criteria will apply to medical devices with CE marks or FDA approvals.

The criteria are:

1. does the device have FDA approval or a CE mark?
2. does the product have a significant history of use?
3. have there been significant problems or regulatory action against the product?
4. does the device contain 'new technology'?
5. is the device of human or animal origin?

If the answers to the first two questions are ‘yes’ and for the last three are ‘no’, evidence from the overseas regulatory agencies will be deemed adequate to determine the quality, safety and efficacy of the device, and the data submitted according to the requirements of DR4 will be used primarily as an element of the post-market vigilance programs.

Changes to the *Therapeutic Goods Regulations* permit reduced evaluation fees for applications to register devices which satisfy the 'Five Point Acceptance Criteria'.

If the device incorporates 'new technology' which has not previously been assessed by the TGA, then this aspect must be evaluated.

Note that if the device is of animal or human origin, a full evaluation of the device will be undertaken.

Regulatory files from European Notified Bodies which can be used to abridge the evaluation process for a registrable device

In recognition of the competence of a European Union Notified Body, designated under Annex XI of the Medical Device Directive (MDD— 93/42/EEC) and Annex 8 of the Active Implantable Medical Device Directive (AIMDD— 90/385/EEC), to perform conformity assessment to the MDD and the AIMDD, the Australian Therapeutic Goods Administration makes the following statements.

1. All therapeutic devices supplied in Australia must have an Australian sponsor.
2. The Australian sponsor is required to submit data, in accord with the document *Australian Requirements for Supply of Therapeutic Devices*, in support of an application for the therapeutic device to be entered on the Australian Register of Therapeutic Goods.
3. Therapeutic devices that are 'registrable', as defined in the *Therapeutic Goods Regulations*, are eligible for an *abridged evaluation* procedure provided specified criteria are met. A reduced evaluation fee will apply to an application for registration submitted in this manner.

For CE marked products,

4. a procedure involving the preparation of a 'regulatory file' by a European Union Notified Body, with the approval of the TGA, may satisfy the criteria for an abridged evaluation. This will reduce the time taken by TGA to enter a 'registrable' therapeutic device on the Australian Register of Therapeutic Goods.
5. The Australian sponsor will arrange for the provision of a 'regulatory file' which must be accompanied by the appropriate application form and fee before it will be considered by the TGA.
6. HIV and HCV in vitro diagnostics and devices of human or animal origin are not eligible for entry on the Australian Register of Therapeutic Goods using this procedure.

Criteria for abridged applications for Registrable Devices based on approvals for supply given under the European Directives

1. European approvals

Registrable devices classified as **Class III or IIb** by application of the rules set out in Annex IX of the Medical Devices Directive (93/42/EEC) or Annex 9 of the Active Implantable Medical Devices Directive (90/385/EEC), must have the following certifications to be considered for an abridged evaluation:

a. Design Examination Certificate to MDD Annex II.4 or AIMDD Annex 2.4;
or
b. Type Test Certificate to MDD Annex III or AIMDD Annex 3;
and
c. Quality Systems Certificate to MDD Annex II.3 or AIMDD Annex 2.3;
or
d. Quality Systems Certificate to MDD Annex V or AIMDD Annex 5;
or
e. Quality Systems Certificate to ISO9001(2)/EN46001(2).

2. Commercial History

The device must have sufficient numbers in service for a period appropriate to the intended use to demonstrate the safety and efficacy of the device.

If there are too few devices in service to demonstrate the safety and efficacy of the device, then the TGA will accept the commercial history of predicate devices whose design and manufacturing technologies have substantial equivalence to those of the submitted device.

Only those in-service or predicate devices that are subject to a mandatory adverse incident reporting system will be considered. The numbers will also be weighed against the regulatory history of the device.

3. Regulatory History

The device must not have been the subject of any adverse regulatory action.

4. Devices of Human or Animal Origin

The device must not contain any material that is of human or animal origin.

5. Technology

Product or manufacturing technologies that are not similar or related to technologies previously evaluated by the Conformity Assessment Branch may require additional evaluation. The need to evaluate new technologies will be assessed by risk analysis for the product or the manufacturing process.

Specifications for the Preparation of a 'Regulatory File'

Contents

1. Commercial history:
    a. number distributed (in countries with vigilance or similar postmarket systems), including those distributed as part of a clinical trial;
    b. time period of distribution in these countries.

2. Regulatory history:
    a. information on the type and nature of any product recalls;
    b. Medical Device Reports (MDRs USA);
    c. vigilance system reports;
    d. approvals in any other countries.

3. Statement that the device contains no component that is of human or animal origin.

4. Description of the device in English including:
    a. Physician's Manual;
    b. unit pack and outer pack labelling;
    c. Promotional Material;
    d. intended use;
    e. comments;
    f. component materials;
    g. Biological safety/ Biocompatibility of the materials at the biological tissue interface;
    h. device technologies;
    i. manufacturing technologies and processes;
    j. manufacturer's risk/benefit analysis;
    k. manufacturer's Declaration of Conformity.

5. Notified Body conformity assessment reports of:
    a. Annexes 2.3.3, 2.3.4, 2.4.3, 2.4.4, 2.5.3, 2.5.4 or 3.4, 3.6 and 5.3, 5.4 of the Medical Device Directive (93/42/EEC) as appropriate; or
    b. Annexes 2.3.3, 2.3.4, 2.4.3, 2.4.4, 2.5.3, 2.5.4 or 3.4, 3.6 and 5.3, 5.4 of the Active Implantable Medical Device Directive (90/385/EEC) as appropriate; including
    c. Summary and component reports (e.g. sterilization, biocompatibility, biological safety, assessment of the manufacturer's risk/benefit analysis, functional safety, constructional safety, electromagnetic compatibility, clinical, etc.)

6. Certification to:
    a. Annexes 2.3 and 2.4 or 3 and 5 of the Medical Device Directive (93/42/EEC) as appropriate; or
    b. Annexes 2.3 and 2.4 or 3 and 5 of the Active Implantable Medical Device Directive (90/385/EEC) as appropriate.

Procedure for an application for entry of therapeutic devices that are registrable in the ARTG using a supporting regulatory file prepared by a European Union Notified Body

1. The Australian sponsor must nominate an authorised officer who is an employee of the manufacturer and who may be contacted by the Therapeutic Goods Administration to obtain responses to questions of a technical nature that may arise from the review of the regulatory file. Copies of correspondence between the manufacturer and the Therapeutic Goods Administration will be provided to the Australian sponsor unless the manufacturer requests that such correspondence be kept in confidence.

2. The holder of the CE certificates issued by the European Union Notified Body is to authorise the European Union Notified Body and the Australian Therapeutic Goods Administration to exchange information as required so that the Therapeutic Goods Administration may satisfactorily establish the quality, safety and efficacy of therapeutic devices to be entered in the ARTG.

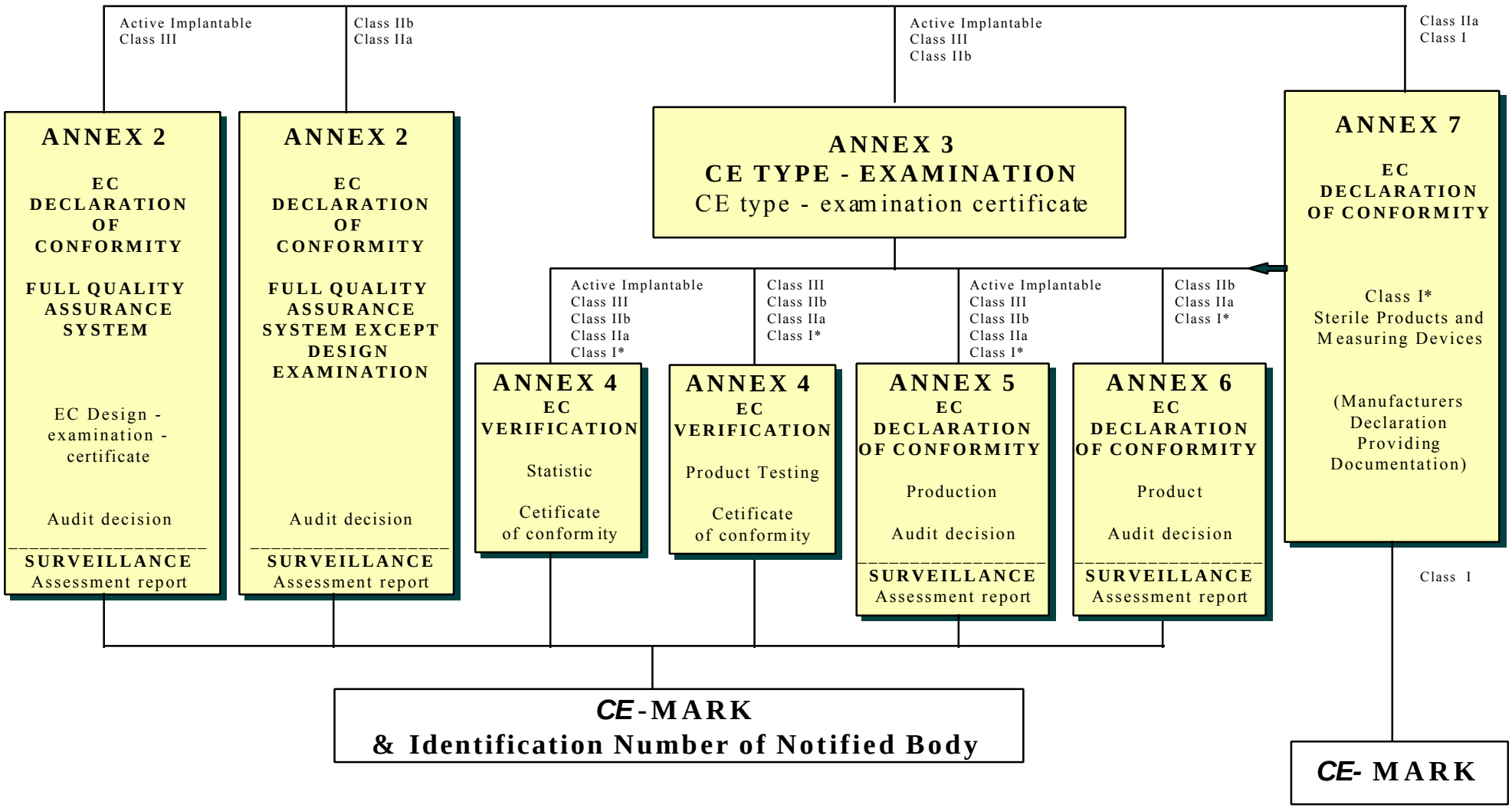
3. The Australian sponsor is to arrange for a European Union Notified Body to submit the regulatory file directly to the Therapeutic Goods Administration.

4. On receipt of the appropriate application fee and form, the application and the regulatory file will be considered by the TGA for evaluation.

5. The TGA will perform a pre-evaluation check and set an evaluation fee.

6. On receipt of the evaluation fee, the data will be evaluated and the device will be considered for entry in the ARTG if the quality, safety and efficacy of the therapeutic device have been satisfactorily established

CONFORMITY ASSESSMENT PROCEDURE + CERTIFICATES



2.5 RISK ANALYSIS

The EU medical device directives require manufacturers of devices to undertake an assessment of the risks inherent in the design and use of individual devices. A standard relating to risk analysis and medical devices (EN 1441) has been released in Europe. It is the intention that this standard will serve as the basis for risk analyses for registrable device submissions.

All submissions for registrable devices to the Conformity Assessment Branch will be required to incorporate a detailed risk analysis section similar to those submitted to European Notified Bodies.

The scope of EN 1441 states:

> This standard specifies a procedure to investigate, using available information, the safety of a medical device, including in vitro diagnostic devices or accessories, by identifying hazards and estimating the risks associated with the device. It is of particular assistance in areas where appropriate harmonised standards are not available or not used.
>
> This standard does not stipulate levels of acceptability, which because they are determined by a multiplicity of factors, cannot by their nature be set down in such a standard.
>
> This standard is not intended to give detailed guidance on risk management.Furthermore, it is not intended to cover decision making processes regarding assessment of the indication and contraindications for the use of a particular device.

Sponsors should also note that the Conformity Assessment Branch considers EN 1441 as the **minimum** requirement for risk analyses for medical device submissions.

As stated in the scope of EN 1441 it is not possible for the TGA to quantify the risk acceptability for each registrable device marketed in Australia. Therefore, sponsors will need to clearly state and justify:

- all assumptions,
- the derivation of all data,
- the use of particular analysis techniques,
- consequential decisions (especially acceptability criteria),

in all registrable device submissions.

2.6 STERILITY

The nature and extent of the information required on the sterile manufacture of the device will depend on the method of sterilization and the criteria for batch release. If batch release of the device is based on measurement and evaluation of physical parameters, rather than the results of testing of product sample or biological indicators, then additional information, specified under Parametric Release below, must also be submitted.

Distinction is also made between batch release on the basis of product sample testing or biological indicator testing (Biological Indicator (BI) Release). (Parametric Release is defined as*declaring product as 'sterile' based on physical process data rather than on the basis of sample testing or biological indicator results;* EN550:1994 *Sterilization of Medical Devices — Validation and Routine Control of Ethylene Oxide Sterilization.*)

Sterile Manufacture

Bioburden Control

An outline of procedures designed to minimise and control the presterilization bioburden must be provided. This must include any microbiological testing of raw materials and in-process testing; presterilization bioburden studies; methods; range of results, specifications and action taken if limits are exceeded.

Additional information is required for Parametric Release or Biological Indicator Release, namely:

- identification of isolates, determination of resistance of isolates to sterilization process; and
- a test for presterilization bioburden, included for every batch. Less frequent testing may be acceptable on the basis of a satisfactory record of previous results.

Environment

A description of the environment within which manufacture and assembly take place is required. This should include details of the supply of HEPA filtered air, where used; access of personnel to the manufacturing area; clothing worn by personnel; regular cleaning and disinfection of the area.
Additional information required for Parametric Release or Biological Indicator Release includes:

- a statement of the frequency; methods; result range; specifications for microbiological monitoring and the action taken if limits are exceeded.

Parameters of the Process

A description of the terminal sterilization process is required. Where the product is terminally sterilized in final sealed containers, the following data are required:

- a statement of the process of terminal sterilization, including the values of all relevant sterilization parameters used in routine production cycles. Depending on the method of sterilization used, this could include: the time of exposure at each stage; gas concentration (in mg/L of chamber volume), liquid sterilant solution composition or concentration; relative humidity; temperature; minimum F_0 or F_H; minimum and maximum irradiation dose; etc. In general, a sterility assurance level (SAL) of at least 10^{-6} should be demonstrated.

Where the product is not terminally sterilized, the following data are required :

- a statement of all processes of sterilization applied to the different components of the product and any equipment associated with the aseptic manufacture. Information on the sterilization processes should include all matters as indicated above. Where any components are sterilized by filtration, test methods for filter integrity must be stated, including the pressure used. A description of the validation of aseptic filling using media fill trials should also be provided.
- a description of the environment in which aseptic stages of manufacture or assembly of the product are conducted, as specified above, including levels of environmental protection provided over critical areas of operation.

Validation of the Process

Information about full validation studies of the sterilization process is required, including details of: studies of empty chamber heat/dose distribution and sterilant penetration into product; lethality studies; results; level of sterility assurance achieved; and frequency and details of revalidation studies.

Additional information required for Parametric Release or Biological Indicator Release includes:

- the revalidation of cycles, annually and after any change to load or process;
- details, for every batch, of the biological indicators used, including a statement of the type, strain of spore, number of spores per indicator, testing for identity and number of spores;
- details of placement of the BI within the load, including the number; placement in relation to, or incorporation within product, and location throughout the chamber; method of extraction from the product, if applicable; cultivation and incubation period of the BI after sterilization;
- if a number of sterilizers which deliver the same process are used for sterilization, each sterilizer should be fully validated, unless equivalence of sterilizers can be satisfactorily demonstrated.

Control of Cycle Parameters

A statement of controls by physical and/or biological means is required. This should include details of the number and placement of thermocouples, measuring devices, biological and/or chemical indicators.

Additional information required for Parametric Release includes:

- information on the calibration and maintenance of recording equipment, which should be conducted at least on an annual basis;
- details of biological indicators where applicable, as specified above;
- if applicable, an additional assurance of process efficacy is required. Information should be supplied on an independent method of providing assurance that the routine sterilizer load has been subject to the proposed process, e.g. measurement of F_o by in-product probes, quantitative or semi-quantitative chemical indicators, direct gas and relative humidity measurements, etc. In some cases microbiological indicators may be acceptable with appropriate controls.

Segregation of Sterilized and Non-Sterilized Items

The means of ensuring that mix-ups do not occur between sterilized and non-sterilized items should be stated, e.g. double-ended sterilizers, colour change indicators attached to every pack.

Package Integrity

Details are required of package integrity testing, including validation procedures for resterilization, if permitted.

Residues

Methods used to minimise and determine residual toxic sterilants are required. Batch release specifications for residue levels of sterilant gases and their by-products should be provided, if applicable.

Review of Sterility Test Data

Where possible, sterility test results should be provided for review, showing a consistently satisfactory result over a 6 to 12 month period.

Batch Release

Criteria for batch release and rejection should be clearly stated. If resterilization is allowed, the suitability of product and packaging should be demonstrated.

A clear distinction should be made between a final product sterility test and a sterility test performed on processed biological indicators, spored portions of the device or dummy devices.

Procedures for Product Sterility Testing

Where applicable, details of sterility testing procedures and description of the environment where sterility testing takes place are required. Sterility testing details of each batch of product should include:

- the number of items tested from each final batch;
- the technique of sterility testing, whether by immersion, wash-through, filling or other;
- the quantity of device tested, whether all or parts of it. For the latter give the reasons for selecting the chosen parts.
- types of media used including fertility tests of media and respective test organisms;
- times and temperatures of incubation of tests;
- precautions taken to eliminate antimicrobial effects of the products (including method validation studies and stasis tests at end of incubation period);
- description of the aseptic environment for sterility testing, including the supply of HEPA filtered air, use of double barrier systems, aseptic gowning of personnel performing the tests, cleaning and disinfection of the area; and
- criteria for release, rejection, retesting or reprocessing, on the basis of the tests for sterility and other in-process sterility controls.

Acceptability of Data

The data presented are assessed against the requirements of:

- the Quality Systems based on ISO 9001/EN 46001; and
- TGO 11 *Standard for Sterile Therapeutic Goods* (see Appendix 15).

The information provided should establish that the methods of sterile manufacture and sterility testing are in accordance with, or equivalent to those found in, the Quality Systems based on ISO 9001/EN 46001 and associated international standards applicable to sterilization procedures.

Reference to Previously Supplied Material

If it is intended that many applications will be made, a 'Sterile Procedures Master File' may be submitted. This document should be a separate volume, titled as above, clearly indexed and consecutively page-numbered right across the volume. The document should NOT be a compilation of Standard Operating Procedures but each relevant chapter should address the points indicated in *Sterile Manufacture* and *Acceptability of Data* above. When submitting an application, the manufacturer should indicate clearly by chapter, page, paragraph and point, which data are directly applicable to the device in question.

2.7 BIOLOGICAL SAFETY AND BIOCOMPATIBILITY TESTING

Sponsors are required to provide details of:

- the biological safety studies performed on the finished device and on representative component samples from the final product or materials;
- the biocompatibility studies, i.e. device-specific functional studies; and
- any other in vitro or in vivo studies carried out on the finished device, especially those relating to long term leachability, stability and durability.

Selection of Tests

Biological Safety

Biological safety tests are a series of generic and basic tests to establish the compatibility of the device materials with the tissues of the patients (recipients) and are intended to determine the absence of harmful effects of materials to ensure a minimum safety level.

Materials used in the manufacture of a device should function as intended without producing adverse local, systemic or allergic responses. An assessment should be made of the materials of manufacture, the final product, intended or unintended additives, leachable substances or degradation products for their relevance in the overall biological acceptability of the device.

The selection of appropriate tests to establish biological safety for a particular device will depend on the intended use of the device, and should take into account the nature of contact, the duration and frequency of contact, and the chemical and physical nature of the generic materials used.

The publication ISO 10993-1:1997; *Biological Evaluation of Medical Devices — Part 1: Evaluation and Testing* discusses the principles of biological safety testing and provides guidelines to the selection of appropriate tests. However it is important to understand that the ISO 10993 series are generic documents which specify a number of acceptable test methods. The choice of specific method suitable for a specific device and the pass-fail criteria for that device are the responsibility of the device-specific standards, and these must be consulted. The potential of a host immune response should also be considered, and appropriate studies carried out. The ISO 10993 series do not yet cover such studies.

It is important also that both the chemical and physical properties of a device be compatible with the method of sterilization and exposure to the body environment.

The following in vitro and in vivo studies on the intact material and/or extracts of the material should be conducted, as appropriate:

Initial Evaluation

Tests for:

- cytotoxicity,
- implantation,
- haemocompatibility,
- systemic toxicity,
- intracutaneous reactivity,
- irritation,
- pyrogenicity,
- sensitization,
- genotoxity.

Special Evaluation

Tests for:

- chronic toxicity,
- carcinogenicity,
- reproductive and developmental toxicity.

In the case of chronic toxicity tests, studies would normally include results for individual animals and be statistically analysed by appropriate methods. The sponsor should provide justification for the tests used and level of investigations performed. Where no test is performed the rationale for not performing that test should be provided.

Information must be provided to demonstrate that the pyrogen or endotoxin level of all sterile therapeutic devices that are intended for contact, directly or indirectly, with the cardiovascular system, the lymphatic system or the cerebrospinal fluid and central nervous system comply with the requirements and test methods in TGO 50*General Standard for Pyrogen and Endotoxin Content of Therapeutic Goods.*

Biocompatibility / Preclinical Studies

Biocompatibility is the ability of the material or device to perform in its intended function with an appropriate host response. The studies are device specific functional assays which are not included nor intended to be included in the ISO 10993 series. Experimental procedures in these studies can provide significant insight into interfacial reactions and therefore also provide valuable safety and efficacy information. For some devices, specific functional testing suggestions or protocols are provided in the respective device chapter in DR4.

The testing performed will depend on the specific device. Where no studies are performed, justification should be provided. Descriptions are required, together with justifications of the applicability of each bench test and in vivo test of the final device, the protocols used and the functional results, ensuring that sufficient batches are sampled and experiments performed for each test to generate statistically reliable results. Sponsors should ensure that the selected testing regimen supports each intended use for the device.

For resorbable materials, a description of the in vivo biokinetics of the biomaterial/device and its components, including the kinetics and biological/pharmacological activity of all degradation and biotransformation products, must be provided under the following headings:

- metabolism,
- absorption,
- excretion,
- distribution,
- other, e.g. protein binding, enzyme induction/inhibitions,
- changes in physical and material properties.

Details of the biodegradation studies undertaken must be provided, including a description of the mode of administration of the material, animals used and parameters studied.

The dynamic properties of the material must be described, as far as is relevant to the intended use of the material, e.g. in vivo changes in mechanical properties with time. Interactions of the material with other compounds and the cellular environment, relevant to the proposed therapeutic usage, should be discussed.

The biological safety and biocompatibility studies performed on the finished biomaterial, including ongoing studies, must address:

- contaminants and possible residues arising from the manufacturing process;
- pyrogen and endotoxin contaminant content;
- details of all in vivo and in vitro biological studies of the biomaterial;
- studies investigating infective contaminants;
- the stimulation of the immune response to biomaterials;
- the in vivo biological/pharmacological activity/biokinetics of the tissue; and
- the immunological potential of the device materials or their degradation products.

In vivo preclinical studies should be conducted on a minimum of ten animals with a minimum follow-up period of one month.

2.8 HUMAN CLINICAL DATA

Investigations involving human subjects may be necessary to demonstrate the safety and effectiveness of a device. A sponsor who wishes to supply the device for the purpose of undertaking clinical investigation in Australia, should seek exemption from entry in the ARTG in accordance with the procedures specified in Chapter 1.24*Access to Unapproved Therapeutic Devices — Clinical Trials and Special Access Schemes.* It covers the conditions to be met and outlines the requirements for preparing an application for exemption for investigational use in humans.

The clinical data submitted by the sponsor must clearly demonstrate that the device:

- will not compromise the clinical condition or the safety of the patients, provided that any associated risks constitute acceptable risks when weighed against the benefits to the patient;
- design and construction are at the generally acknowledged state-of-the-art in terms of safety and efficacy;
- achieves performances intended by the manufacturer;
- is not adversely affected by stresses which can occur during normal conditions of use; and
- does not cause any undesirable side-effects that would constitute an unacceptable risk when weighed against the performance intended.

The general requirements for clinical data are set out below and where a particular paragraph is not considered to be relevant to a predicate device, the sponsor is required to provide a brief explanation of the reasons.

Ethical Standards

Clinical investigations must be designed and conducted according to acceptable ethical standards set out in the current edition of the *World Medical Association Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects.* Consideration should also be given to the standards referred to in the NHMRC *Statement on Human Experimentation and Supplementary Notes,* available from the NHMRC Publications office (ph: 02 6289 7646) and the TGA document*Guidelines for Good Clinical Research Practice* available from the TGA Publications Office ph: 1 800 020 653.

Data from well conducted clinical trials should be amenable to independent assessment according to accepted scientific methods to establish the safety and effectiveness of the device under investigation. The data may be generated from trials conducted in Australia or internationally.

Data to be Submitted

The information provided in this section should comprise a stand-alone document which will contain all of the information needed for an evaluator to reach a conclusion regarding the clinical safety and effectiveness of the device. An 'expert report' written by an appropriate and impartial authority in the relevant field, must be included.

In addition, this section of the submission should include summary data as specified below to establish functional and preclinical testing. It should outline the results and conclusions from this background information which forms the basis for the clinical investigation in humans.

Safety and Effectiveness Data

A summary including the following is required:

- general details of the device,
- a description of the device and its functions,
- materials and construction used in the device,
- GMP status,
- details of preclinical safety testing, including mechanical, in vitro, and in vivo testing together with results and conclusions.

Regulatory and Commercial History

Information is required on the following aspects of the device:

- the commercial history including when the device first became available for commercial use and the number of devices sold in Australia and world-wide;
- the overseas regulatory status, in particular the current status in the European Union (EU) and US Food and Drug Administration Regulations; and
- any details of any adverse regulatory action, such as recalls or incident reports.

Where the application is based on substantial equivalence to a predicate device, the information above shall be provided for the equivalent device.

Clinical Investigation

The sponsor shall provide a detailed report of the clinical investigation in accordance with the International Standard ISO 14155 *Clinical Investigation of Medical Devices on Human Subjects.* For some device groups (e.g. heart valves), additional clinical data must be provided in accordance with the current ISO Standard on that device group. This additional information must be appended to the clinical investigation report.

The Standard(s) used should be clearly stated and all information provided should be cross-references to the Standard(s).

Postmarket Surveillance

- Give the details of procedures for maintaining a database of patient and device identification.
- Give details of the system for monitoring device performance.
- Give details of the system for obtaining and processing problems with the device.

Refer also to Chapter 1.6 *Postmarket Compliance Programs*

HIGH LEVEL REGISTRABLE DEVICES

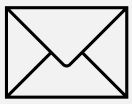
The following chapters specify the additional information to be supplied for each registrable device. Please refer to the checklist in the individual device categories for a summary of the information necessary for an application.

Specific high level Registrable device policies	Chapter
Active Implantable Medical Devices (AIMD)	2.9
Animal origin devices	2.10
Breast prostheses (not saline or water)	2.11
Drug infusion systems	2.12
Extracorporeal therapy systems	2.13
Heart valve prostheses	2.14
Human origin devices	2.15
Intraocular lenses (IOL)	2.16
Intraocular viscoelastic fluids (IOF)	2.17
Intrauterine contraceptive devices (IUCD)	2.18

These requirements are in addition to the details specified in Chapter 2.1 *Information Applicable to all Registrable Devices*.

Sponsors should include additional information as appropriate. The TGA may seek additional information if necessary.

Sponsors should contact the TGA and if necessary request a meeting if they have difficulty in interpreting the information in DR4. Sometimes, submissions are not supported by sufficient appropriate data, and their evaluation is delayed. This can be prevented if sponsors discuss the TGA's requirements with staff of the TGA, before sending in their submissions. Sponsors who do not have the resources to prepare a submission may wish to consider using a consultant.



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2.9 ACTIVE IMPLANTABLE MEDICAL DEVICES (AIMD)

Any medical device which relies on an electrical energy source or any source of energy other than that directly generated by the human body or gravity for its operation and performance, and is designed to be implanted, in full or in part, by surgical or medical operation into the human body or by medical intervention into a natural orifice, and which is intended to remain in place after the procedure, is categorised as an Active Implantable Medical Device. These include, but are not limited to:

- Implantable Central Nervous System Pulse Generators,
- Diaphragmatic/Phrenic Nerve Stimulators,
- Carotid Sinus Stimulators
- Intra-cerebellar/Subcortical and Deep Brain Stimulators,
- Cerebellar Stimulators,
- Vagal Nerve Stimulators,
- Implantable Drug Infusion Pumps,
- Cardiac Pacing Systems.

Although not active, all permanently implanted accessories such as leads and lead adaptors, extensions, caps and plugs, catheters and ports, for use with active implantable devices, are classified as registrable devices.

Reference Documents

ANSI/AAMI NS15-1995 Implantable Peripheral Nerve Stimulators.
ANSI/AAMI NS14-1995 Implantable Spinal Cord Stimulators.
European Council/ Directive 90/385/EEC of 20 June 1990 concerning active implantable medical devices.
EN45502-1 Active implantable medical devices. Part 1: General requirements for safety, marking and information to be provided by the manufacturer.
EN45502-2 Active implantable medical devices. Part 2: Particular requirements for active implantable medical devices intended to treat bradyarrhythmia (Pacemakers).
EN45502-3 Active implantable medical devices. Part 3: Particular requirements for implantable cardioverter defibrillators and the functions of active implantable medical devices intended to treat tachyarrhythmia.
ISO 5841-3 IS-1/VS-1 Standard, ISO 11318 DF-1 Standard.

Copies of Australian and International Standards available from Standards Australia National Sales Centre

ph: 1800 029 955 or
02 9746 4600
web site http://www.sic@saa.sa.telememo.au

Contact details for European Directives is available in Chapter 1.18 *Mutual Recognition Agreement with Europe.*

Each registrable device submission must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

General Details

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Risk Analysis

Refer to Chapter 2.5 *Risk Analysis.*

Table of Equivalence

A Table of Equivalence is applicable to a new device if the device submitted for registration has developed from, and has similarities to, a device which is currently registered and previously evaluated for supply in Australia.A Table of Equivalence shall indicate the differences and similarities in the following areas between the devices, where applicable:

- intended use;
- the type and characteristics of any internal power supply;
- the type of technology used in the implementation of the electronic circuitry;
- the general physical layout of the internal electronics;
- the characteristics of any sensors or detectors;
- the mechanical design of the device enclosure;
- the design of any input/output connector assembly/connection terminal and the design and characteristics of the male/female connectors associated with it;
- the functional structure of the electronic circuitry of the device;
- the available modes in which the device can operate, if more than one preprogrammed parameter;
- the available range for all programmable parameters;
- the type of communication between the device and any external device/programmer;
- the specification of any resident and/or transferable software and the identification of software versions;
- the specification of any active non-implantable part of the device;
- the design of the active electrode;
- design of the tissue fixation mechanism of the distal end of an electrode;
- the design of the lead body and conductors;
- the type and characteristics of the lead connector;
- the design, composition and function of any drug delivery incorporated into the device;
- any constituent materials critical to the proper functioning of the device;
- the biocompatibility of materials in contact, or with potential to come into contact, with body tissues and fluids;

- the details on dimensions of the lead or adaptor;
- whether the lead/adaptor is an active conductor or a passive part;
- the manufacturing process;
- the sterilization process;
- packaging;
- the mechanism of regulation of the delivery of solutions;
- the mechanisms for the refilling of any internal reservoir;
- the safeguard mechanism to prevent overinfusion or overdose.

Commercial and Regulatory History

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice

General details on the manufacturing process shall be provided, including:

- any details on site interfaces (i.e. the transfer of products' ongoing manufacture from one site to a different site);
- any details on any subassemblies provided by third party manufacturers.

The principal and any alternative releasing manufacturer for an active implantable device or lead/implantable accessory shall provide evidence to satisfy the requirements of ISO9001/EN46001 for sterile/mechanical/electrical manufacturing. For overseas manufacturers, refer to Appendix 10, *GMP — Standard of Overseas Manufacturers*.

Reporting Conditions

Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance

Refer to Chapter 1.6 *Postmarket Compliance Programs.*

Samples

Submissions should include a sample of the device, or device family, that will allow the construction and layout of the device to be examined. The sample should be supplied in the original packaging material including sterile trays and external packaging. If requested, the sample device will be returned to the sponsor on completion of the evaluation.

Labelling

Copies of the labelling to be supplied in Australia shall be included in the submission for:

- the sterile packaging of the active implant, lead or implantable accessories,
- the external package of the active implant, lead or implantable accessories,
- the enclosure of the active implant, lead or implantable accessories,
- the radio opaque ID of the active implant, lead or implantable accessories,
- any additional packaging for literature, cards, etc.,
- any templates for the location of the implant or associated ports.

The submission must clearly indicate which label corresponds to the unit and outer packs. Labelling will be evaluated against TGO 37*General Requirements for Labels for Therapeutic Devices* (see Appendix 16).

Design / Materials / Testing

Design / Construction

The relationship between components will be examined to assess if any mechanical or electrical interference is likely to arise. The quality of connections, reliability of the source of energy, or where appropriate, the hermetic seal will be considered. The assembly processes will be examined as part of the manufacturing evaluation.

For active implantable devices the submission should include a description of the device including:

- the description and general block diagram of embedded software, programmer application software, programmer operating system software and the interaction of these functional blocks; and
- X ray images.

For leads and implantable accessories the following information is required:

- whether the accessory is an active conductor or a passive part;
- the design of all electrodes;
- the design of the tissue fixation mechanism at the distal end;
- the design of the lead body and conductors;
- the type and characteristics of the lead connector;
- the composition and function of any drug eluting mechanism incorporated into the lead;
- details of dimensions of the lead or adaptor;
- engineering drawings for the whole device and for its main components, showing the dimensions of the assembled device and any accessories;
- details on assembly;
- reliability studies.

For implantable drug infusion pumps, the submission must describe:

- details on any injection port or similar accessory;
- the mechanism for monitoring the current status of the device.

The design of the device will be examined to check that it conforms to safety principles acknowledged as state-of-the-art, even if the device has been modified to implement certain specifications. State-of-the-art safety standards are described in the documents referenced in DR4 and in other relevant manufacturer specific or voluntary standards.

The submission should indicate that the design of the device is such that the specifications intended by the manufacturer will be met under normal conditions of use and provided the device is used within the period specified and transported in accordance with the directions.

Materials

The submission should indicate if any material of the device is critical to the safety and effectiveness of the device (e.g. seals preventing ingress of fluids, electrical contacts on which functionality depends, springs or bellows regulating the flow of fluid, etc.). Sponsors are required to provide a description, specifications and source of such material.

For leads and implantable accessories, a description, specifications and source of all constituent materials must be provided. Evidence is required that exposure of such materials to the environment and working conditions for which the lead or accessory is intended does not degrade the insulation, conductors or any other essential part of the lead,such that its function is significantly compromised.

All materials that come in direct contact with biological tissues, or with substances that are to be administered by the device, will be evaluated for toxicity and mutual compatibility as part of the Biological Safety and Biocompatibility evaluation described later in this chapter, with reference to Chapter 2.7 *Biological Safety and Biocompatibility Testing.*

For implantable pumps, manufacturers should ensure that materials coming into contact with the drug/solution are compatible with the infusate and do not affect the stability of the infusate.

Testing

The evaluation of tests will take into consideration any test conducted by the manufacturers or their subcontractors and any tests undertaken by TGA as part of a Postmarket Compliance Program.

Qualification Testing

This includes all laboratory and bench testing of either the assembled device or its components parts including the functionality of any associated software and the rationale for the acceptance criteria on the test.

For active implantable devices the submission should include at least, but not be limited to, the following qualification tests:

- power supply testing and life expectancy;
- critical electronic integrated/discrete component validation;
- functional validation of the device, including the accuracy of any delivered flow or dosage of solutions;
- mechanical validation of the assembled device;
- mechanical validation of the connector block if applicable;
- functional validation of the generator;
- functional validation of the telemetry system;
- functional validation of any sensors and/or detectors;
- longevity studies for the implanted device;
- reliability studies and their conclusions and rationale;
- environmental testing;
- any studies of the reliability of the device in long-term use, including possible adverse environmental effects.

The submission should also include

- any documented results of tests to verify the above specifications, and details of test methods used;

- a report and copies of any Certification showing the susceptibility of the device to radiated electromagnetic interference and conducted electrical interference.
  The spectrum of interference shall cover at least:
  - injected power frequencies at 50, 60 and 400 Hz,
  - low frequency magnetic fields at 50 Hz and 60 Hz,
  - pulsed waveforms with carrier frequencies at 450, 2450 and 3100 MHz,
  - 800 MHz analogue,
  - 900 MHz PLS.

Other sources of potential interference that should be considered include:

- conducted and radiated interference from electrosurgical generators,
- radiated interference with the characteristics of cellular phone systems that are in current use in Australia,
- retail anti-theft detection units,
- occupationally related exposures.

For leads and implantable accessories

the submission should include at least, but not be limited to, the following qualification tests:

- material effects of sterilization;
- connector maximum insertion and withdrawal force;
- connector deformation due to set screw forces;
- DC resistance;
- dry ageing (temperature);
- connector insertion force after ageing;
- fluid ingress (inked saline soak);
- minimal electrical impedance between conductive elements;
- fatigue testing accelerated flex test for mechanical fatigue of critical segments of the assembled lead, until failure, unless a known proven design is used. Comparison should be made against known marketed leads of similar characteristics, or photographs or equivalent of fracture or failure points;
- insulation dielectric breakdown;
- proximal and distal pull test;
- lead/joint tensile test;
- crimped connection pull test;
- distal end stiffness test as a predictor of myocardial penetration and perforation. Comparison should be made against known marketed leads of similar characteristics.

For Implantable Drug Infusion Pumps

the submission should include at least, but not be limited to, the following qualification tests:

- the expected life of refilling septums or equivalent mechanisms;
- flow rate delivery characteristics;
- maximum line pressures.

Manufacturing / Quality Control / Sterility

Manufacturing *For Leads and Implantable Accessories*

General details and flow charts illustrating the manufacturing process shall be provided including further details on critical steps and any site interfaces (transfer of products or components from one site to a different site). Details are required of any subassemblies provided by third party manufacturers and quality control procedures for acceptance. Details are required on any step of manufacturing introducing residual stress and/or flaws in the material which can impair the longevity of the lead.

Quality Control

In rare circumstances where quality systems certification may have lapsed and a re-certification is imminent, supply may be allowed to continue where appropriate, on a batch by batch basis. The batch reports will be evaluated under this category.

Sterility

Details on the sterilization process for the device are required. Criteria are necessary for the disposal or return to the manufacturer of devices when sterility has been compromised, e.g. by a damaged packaging or exposure of the fluid path. The TGA does not consider that it is appropriate to resterilize a sterile device where sterilization processes have not been validated and approved by the TGA.

Where specific cleaning and/or disinfection solutions or accessories are required for the device, the submission should describe the containers, composition of solutions, any equipment required and specifications. Refer to Chapter 2.6*Sterility.*

Biocompatibility / Preclinical

Biological Safety and Biocompatibility

For Leads and Implantable Accessories

Details of the study of the effects of any drug incorporated into a lead electrode must also be provided. Where no studies are performed, justification should be provided.

Preclinical Studies

Details of preclinical studies in animals for active implantable devices are to be provided, where these have been conducted, to demonstrate the safety and efficacy of a new therapy, or an extension of a therapy, or an indication for use.

Refer to Chapter 2.7 *Biological Safety and Biocompatibility Testing*

Ch. 2.9 Active Implantable Medical Devices (AIMD)

Please include this completed checklist with your submission

A tick indicates information that is to be supplied as part of the submission

Fee Structure	Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.9	Reference Vol/Page
	General Details	✓		/
	Risk Analysis	✓	✓	/
	Table of Equivalence #	✓	✓	/
	Commercial and Regulatory History	✓		/
	GMP	✓		/
	Reporting Conditions	✓	✓	/
	Postmarket Surveillance	✓		/
	Samples	✓	✓	/
Design/	Design and Construction	✓	✓	/
Materials/	Materials	✓		/
	Labelling	✓	✓	/
	Packaging	✓		/
	PI/Instructions for Use/PM **	✓		/
				/
Testing	Testing	✓		
			✓	
Manufacturing/	Manufacturing	✓	✓	/
Quality Control/	Quality Control	✓	✓	/
Sterility	Sterility	✓	✓	/
Biocompatibility/	Biological Safety/Biocompatibility Testing	✓	✓	/
Preclinical (in vivo)	Preclinical (in vivo)	✓	✓	/
Human Clinical Data	Human Clinical Data	✓		/

\# to be provided if equivalence to a predicate device is beingclaimed

** Product Information/Instructions for Use/Promotional Material

Ch. 2.9 Active Implantable Medical Devices (AIMD) — Table of Equivalence

If Equivalence is being sought for a reduction in evaluation fees
*please include this **completed** Table of Equivalence with your submission*

Please indicate where *Predicate* and *Equivalent* Information is supplied, and reference details within the submission

* *Preclinical (in vivo) studies & Human Clinical Data should substantiate changes to the indication for use of the new product*

Fee Structure	Evaluation Categories	✓ Registered Predicate Device	✓ Equivalent Information New Device	Reference Vol/Page
Design/	Design and Construction	_____	_____	/
Materials/	Materials	_____	_____	/
	Labelling	_____	_____	/
	Packaging	_____	_____	/
	PI/Instructions for Use/PM #	_____	_____	/
Testing	N/A			
Manufacturing/	Manufacturing	_____	_____	/
Quality Control/	Quality Control	_____	_____	/
Sterility	Sterility	_____	_____	/
Biocompatibility/	Biological Safety/Biocompatibility Testing	_____	_____	/
Preclinical (in vivo)	Preclinical (in vivo)*	_____	_____	/
Human Clinical Data	Human Clinical Data*			/

\# Product Information/Instructions for Use/Promotional Material
* May be requested by the TGA during the evaluation process

2.10 ANIMAL ORIGIN DEVICES

Sponsors are advised to contact the TGA before submitting an application if confirmation of submission requirements is needed. Reference should be made to Appendix 11, *Human or Animal Origin Devices.*

Evaluation of animal-derived tissue is restricted to therapeutic devices or components of devices which are of animal origin for use in the body or for application to broken skin, other than devices that:

- are manufactured using animal derived waxes; or
- incorporate heparin, unless heparin is being delivered as a drug; or
- are sutures conforming to a standard determined under Part 2 of the Act; or
- are made from sintered hydroxyapatite; or
- incorporate gelatin that conforms to generally accepted pharmacopoeial

Refer to Chapter 3.3 *Animal Derivatives Contained in Listed Devices.*

Requirements for registration of intraocular viscoelastic fluids which are of animal origin are outlined in Chapter 2.17 *Intraocular Viscoelastic Fluids.*

Each registrable device submission must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

General Details

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Risk Analysis

Refer to Chapter 2.5 *Risk Analysis*.

Table of Equivalence

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Commercial and Regulatory History

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice

Refer to Chapter 1.19 *Good Manufacturing Practice.*

Reporting Conditions
Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance
Refer to Chapter 1.6 *Postmarket Compliance Programs.*

Samples
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Quarantine — *For Imported Devices Only*
Evidence of the issue of an Import Permit in accordance with the *Quarantine Act (1908)* must be provided. Compliance with the *Quarantine Act (1908)* is a function of the Australian Quarantine and Inspection Service (AQIS) of the Department of Primary Industries and Energy (DPIE). Sponsors are required to obtain an Import Permit for importation of human, animal or plant material. Refer to Chapter 1.4 *Quarantine Requirements (AQIS).*

Design/Materials/Testing

Labelling
The outer package label should make a statement indicating the device contains material of animal origin (e.g. bovine, ovine etc.)

Product Literature
The following statement, or one of similar intent, must be included in information provided separately to patients:

> "This device is derived from animal tissue and although care has been exercised in its manufacture to minimise pathogen content, a potential risk is present and absolute freedom from infective agents cannot be guaranteed."

Manufacturing / Quality Control / Sterility

Refer to Chapter 2.6 *Sterility*

Source Materials and Risk of Infectivity — Animal Materials
If more than one type of animal-derived material is used to manufacture this therapeutic good, complete a copy of this declaration below for each type.

Part 1: Virus Control
This questionnaire applies to <u>all</u> animal-derived reactants or therapeutic goods not exempted in Appendix 11, *Human or Animal Origin Devices.*

Source
Specify

- the name of the animal material or ingredient used (e.g. collagen, pericardium, serum, trypsin, urine, etc.) and the tissue or organ, if applicable, from which it is obtained;

- whether the material or ingredient conforms to a standard as published in monographs such as BP, EP, USP;
- the animal species from which the material or ingredient is sourced.

National Controls

Provide full details, including certification and evidence of national controls (e.g. veterinary inspections, notifiable diseases, surveillance procedures, etc.) applicable to the subject animal species within the country in which the animals resided. The following must be provided:

- a list of the notifiable diseases of the animal species in its country of origin;
- details of vaccination, disease outbreaks in the facility, and any action taken in the event of an outbreak;
- whether the animals are examined pre- and post-mortem and are approved for human consumption;
- the name(s) and address(es) of the abattoir(s), details of the site inspection or approval by the national regulatory authority and whether it is certified as suitable for preparation of meat for human consumption;
- a declaration listing the national controls with which the donor animals comply and any relevant conditions of animal husbandry intended to reduce the incidence of disease.

Processing

The submission must provide information and data, including evidence of compliance to standards and monographs, etc., if applicable, for the material or ingredient within the country of manufacture, including the following:

- the production process of the ingredient including any validated step designed to inactivate or clear infectious agents including viruses; discussion of the steps in manufacturing, if any, undertaken to comply with advice provided in *Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses — CPMP/BWP/268/95* (see Appendix 11);
- the manufacturing process of the therapeutic product, describing in detail any validated virus inactivation or clearance step(s); discussion of the steps in manufacturing, if any, undertaken to comply with advice provided in *Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses — CPMP/BWP/268/95*.
- the tests that are done on the intermediates or on the final product to ensure that no adventitious virus is present;
- where relevant, the methods applied to sanitise the production plant to ensure contamination does not occur between batches;
- an assurance that animal-derived components from any other source are not used, and that the supplier will not be changed without prior approval from the TGA.

Information about the sterilisation of the finished therapeutic good should be supplied with the 'Sterility' component of the submission.

Part 2: Control of agents causing spongiform encephalopathies

This questionnaire applies to bovine, ovine & caprine (cattle, sheep & goat) reactants and therapeutic goods.

Country of origin is defined as country or countries in which semen for artificial insemination was sourced and animals were born and reared.

Source

Specify

- the name and category of tissue or organ (according to *Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products — CPMP/BWP/877/96,* see Appendix 11) used in the manufacture of the therapeutic good;
- the country of origin of the animal species (include a statement on the source of semen if females were artificially inseminated);
- age of the animals from which tissue is sourced;
- whether the tissue is derived from animals which were, until slaughter, members of a closed herd. If so, provide details of the conditions of herd closure including the length of time of closure; support with relevant documentation.

Closed herds —herds that are 10 years old, or closely monitored herds with documented breeding history, freedom from disease, regular veterinary inspections and feeding habits which exclude animal-derived protein supplements, are ideal sources of animal materials. Raw materials obtained from these types of herds are highly recommended for the manufacture of pharmaceuticals and medical devices.

- procedures of slaughter and tissue retrieval, conditions available in abattoir, e.g. quarantine of selected animals and tissues, prevention of cross-contamination (including the appropriate cleaning or sterilization of instruments equipment between carcasses);
- conditions of transport and intermediate manufacturing sites, if any;
- the company policy on the segregation and disposal of source material which does not meet the raw material specifications.

National Controls

Provide full details, including the certification and evidence of national controls (e.g. feed importation bans, specialised veterinary inspections, surveillance procedures, etc.) applicable to the subject animal species within the country of origin, addressing each of the following:

- controls on animal importation;
- controls on the importation of animal-derived feed;
- ratio of cattle:sheep:goats;
- incidence of BSE and scrapie (rate per calendar year) since 1986;
- type of feed provided to livestock, include whether animal-derived protein and meal are consumed;
- location of the source herd in relation to BSE and scrapie cases, if any;
- specific veterinary inspection (macroscopic or microscopic) of animals for medical products and food.

Processing

Provide information and data about the specific steps taken during manufacture which are intended to minimise the potential infectivity of agents causing the transmissible spongiform encephalopathies, addressing each of the following:

- justification of tissue pooling, if applicable, and methods of control used to aid tracking from finished product to source animals;
- manufacturing steps intended to reduce or inactivate a potential infective titre of agents causing transmissible spongiform encephalopathy. Documented validation of each procedure must be submitted to support its efficacy.
- discussion of the steps of manufacture, if any, undertaken to comply with the advice provided in the *Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products — CPMP/BWP/877/96* (see Appendix 11).

Biocompatibility / Preclinical

Biological Safety and Biocompatibility Testing

The submission must provide specifications for raw materials, reagents and final product and the methods of determination for each; include levels and nature of impurities associated with the initial and final steps of manufacture; and provide protocols for each critical production step in the tissue manufacture. Refer to Chapter 2.7 *Biological Safety and Biocompatibility Testing*.

Testing — Stability Testing and Shelf Life

A detailed description is required of stability testing and the rationale for the determined shelf life.

Human Clinical Data

Refer to Chapter 2.8 *Human Clinical Data*

Ch. 2.10 Animal Origin Devices

Please include this completed checklist with your submission

A tick ✓ indicates information that is to be supplied as part of the submission

Fee Structure	Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.10	Reference Vol/Page
	General Details	✓		/
	Risk Analysis	✓		/
	Table of Equivalence #	✓		/
	Commercial and Regulatory History	✓		/
	GMP	✓		/
	Reporting Conditions	✓		/
	Postmarket Surveillance	✓		/
	Samples	✓		/
	Quarantine ##	✓	✓	/
Design/	Design and Construction			/
Materials/	Materials			/
	Labelling	✓	✓	/
	Packaging	✓		/
	PI/Instructions for Use/PM **	✓	✓	/
				/
Testing	Testing			
Manufacturing/	Manufacturing	✓	✓	/
Quality Control/	Quality Control	✓		/
Sterility	Sterility	✓		/
Biocompatibility/	Biological Safety/Biocompatibility Testing	✓	✓	/
Preclinical (in vivo)	Preclinical (in vivo)	✓		/
Human Clinical Data	Human Clinical Data	✓		/

\# to be provided if equivalence to a predicate device is being claimed

should comply with AQIS requirements for imported devices containing human and animal derived material

** Product Information/Instructions for Use/Promotional Material

Ch. 2.10 Animal Origin Devices — Table of Equivalence

If Equivalence is being sought for a reduction in evaluation fees
*please include this **completed** Table of Equivalence with your submission*

Please indicate ✓ where *Predicate* and *Equivalent* Information is supplied, and reference details within the submission

Fee Structure	Evaluation Categories	✓ Registered Predicate Device	✓ Equivalent information New Device	Reference Vol/Page
Design/	Design and Construction	_____	_____	/
Materials/	Materials	_____	_____	/
	Labelling	_____	_____	/
	Packaging	_____	_____	/
	PI/Instructions for Use/PM #	_____	_____	/
Testing	N/A			/
Manufacturing/	Manufacturing	_____	_____	/
Quality Control/	Quality Control	_____	_____	/
Sterility	Sterility	_____	_____	/
Biocompatibility/	Biological Safety/Biocompatibility Testing	_____	_____	/
Preclinical (in vivo)	Preclinical (in vivo)	_____	_____	/
Human Clinical Data	Human Clinical Data			/

Product Information/Instructions for Use/Promotional Material

2.11 BREAST PROSTHESES (NOT SALINE OR WATER)

Implantable breast prostheses whichare constructed of an outer polymeric shell and contain an inner filling material that is not water or saline (e.g. silicone gel filled, or soya bean lipid filled prostheses) are classified as high level registrable devices.

Each registrable device submission must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

General Details

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Risk Analysis

Refer Chapter 2.5 *Risk Analysis.*

Table of Equivalence

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Commercial and Regulatory History

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice

Refer to Chapter 1.19 *Good Manufacturing Practice.*

Reporting Conditions

Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance

Refer to Chapter 1.6 *Postmarket Compliance Programs*, and

- address the issue of device marking to enable identification of the make, model and batch number of the implant by some imaging modality;
- provide details of procedures for maintaining a database of patient and device identification;
- provide details of the system for obtaining and processing problems with the device.

Samples

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Design / Materials / Testing

Design / Construction

A description of the design of the breast prosthesis is required, e.g. shape, volume/s, seams/seals, surface characteristics, valve, nature and general properties of the filling material.

Materials

Details of all raw materials, their specifications and purity must be provided. If the shell or filling materials are of animal or human material, the requirements relating to biological materials must be satisfied, as set out in Chapter 2.10*Animal Origin Devices* or Chapter 2.15 *Human Origin Devices,* whichever is relevant.

Product Information / Instructions for Use / Promotional Material

The product literature should be provided and should include:

- an implant identification card for the patient; and
- at least two self adhesive labels with the implant details necessary for product identification. Advice should be given that the labels are to be attached to the hospital's and surgeon's records of the patient.

Manufacturing / Quality Control / Sterility

Manufacturing — Validation Testing

Performance Characteristics — Integrity of the Shell Material

Details must be provided of all test protocols, results and conclusions of the following tests and studies on the finished material:

- shell surface characteristics/pore size/diffusion potential;
- impact resistance;
- tear resistance;
- strength of seals and seams;
- rupture rates;
- resistance to abrasion;
- elastic modulus and tensile properties; and
- fatigue testing and ageing.

If resterilization is an option, provide details of the effect of the process on the stability of the device.

Performance Characteristics — Integrity of the Valve

To demonstrate the reliability of the valve, if fitted, and any associated inflation mechanism, provide details of the test protocol, results and conclusion(s).

Physical Properties of the Inner Filling Material

The submission must provide details of the physical characteristics of the filling material, e.g. viscosity, cohesiveness, radio-opacity.

Biocompatibility / Preclinical

Biological Safety and Biocompatibility Testing

Complete details should be submitted of protocols used in assessing Biological Safety and Biocompatibility, raw data and their analyses, if:

- the raw materials have not been previously evaluated and marketed for this proposed indication in Australia, or
- a change has occurred in the material processing during manufacture.

If the materials have been previously marketed in Australia for implants, list the products in which they are used. Details of the immunological potential of the materials must be provided. Humoral and cell mediated responses should be investigated and reported to the TGA. Refer also to Chapter 2.7 *Biological Safety and Biocompatibility Testing.*

Human Clinical Data

The clinical data should include the assessment of both systemic and local responses of patients participating in the trials. The assessment should also take into consideration effects which may be related to the different indications of use. Refer to Chapter 2.8*Human Clinical Data.*

Ch. 2.11 Breast Prostheses (not saline or water)

Please include this completed checklist with your submission

A tick ✓ indicates information that is to be supplied as part of the submission

Fee Structure	Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.11	Reference Vol/Page
	General Details	✓		/
	Risk Analysis	✓		/
	Table of Equivalence #	✓		/
	Commercial and Regulatory History	✓		/
	GMP	✓		/
	Reporting Conditions	✓		/
	Postmarket Surveillance	✓	✓	/
	Samples	✓		/
	Quarantine ##	✓		/
Design/	Design and Construction	✓	✓	/
Materials/	Materials	✓	✓	/
	Labelling	✓		/
	Packaging	✓		/
	PI/Instructions for Use/PM **	✓	✓	/
				/
Testing	Testing	✓	✓	
Manufacturing/	Manufacturing	✓	✓	/
Quality Control/	Quality Control	✓		/
Sterility	Sterility	✓		/
Biocompatibility/	Biological Safety/Biocompatibility Testing	✓	✓	/
Preclinical (in vivo)	Preclinical (in vivo)	✓		/
Human Clinical Data	Human Clinical Data	✓	✓	/

\# to be provided if equivalence to a predicate device is being claimed

should comply with AQIS requirements for imported devices containing human and animal derived material

** Product Information/Instructions for Use/Promotional Material

Ch. 2.11 Breast Prostheses (not saline or water) — Table of Equivalence

If Equivalence is being sought for a reduction in evaluation fees
*please include this **completed** Table of Equivalence with your submission*

Please indicate ✓ where *Predicate* and *Equivalent* Information is supplied, and reference details within the submission

* *Preclinical (in vivo) studies & Human Clinical Data should substantiate changes to the indication for use of the new product*

Fee Structure	Evaluation Categories	✓ Registered Predicate Device	✓ Equivalent information New Device	Reference Vol/Page
Design/	Design and Construction	_____	_____	/
Materials/	Materials	_____	_____	/
	Labelling	_____	_____	/
	Packaging	_____	_____	/
	PI/Instructions for Use/PM **	_____	_____	/
Testing	N/A			
Manufacturing/	Manufacturing	_____	_____	/
Quality Control/	Quality Control	_____	_____	/
Sterility	Sterility	_____	_____	/
Biocompatibility/	Biological Safety/Biocompatibility Testing	_____	_____	/
Preclinical (in vivo)	Preclinical (in vivo)	_____	_____	/
Human Clinical Data	Human Clinical Data			/

** Product Information/Instructions for Use/Promotional Material

2.12 DRUG INFUSION SYSTEMS (POWERED, NON-IMPLANTABLE)

These non-implantable devices are intended to regulate the flow of liquids into the patient under positive pressure generated by the pump.

However, the following devices are not powered drug infusion systems:

- equipment specifically intended for angiography or enteral infusion or extracorporeal circulation of blood;
- implantable or single use devices (implantable pumps are active implants);
- simple and metered dose syringes;
- infusion-giving sets which do not have automatic means of controlling delivery;
- the type of non-implantable infusion devices where the flow rate is regulated by means of a calibrated bore restrictor and where the flow rate is fixed and cannot be adjusted.

Administration sets are registrable devices if they can only be used with a particular infusion pump or infusion controller in order to maintain its safety and effectiveness. Administration sets are evaluated only for their effect on the resulting flow rate of infusate. In this case, administration sets are grouped as 'products' under the respective infusion pump registration.

Administration sets which are not specifically claimed for use with a particular infusion pump or infusion controller are **listable** devices.

Reference Documents

Australian Standard AS/NZS3200.1.1:1995 *Approval and test specification — Medical electrical equipment, Part 1.1 General requirements for safety — Collateral Standard: Safety requirements for medical electrical systems* (based on IEC Standard 601-1-1).
IEC-601-2-24 *Particular Requirements for Infusion Pumps and Controllers.*
IEC 601-1-2, *Medical electrical equipment, Part 1: General requirements for safety 2. Collateral Standard: Electromagnetic Compatibility — Requirements and tests*.
Draft IEC 601-1-4 *Medical electrical equipment, Part 1 General requirements for safety 4. Collateral Standard: Safety requirements for programmable electronic medical systems*.

Each registrable device submission must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

General Details

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*.

Risk Analysis

Refer to Chapter 2.5 *Risk Analysis*.

Table of Equivalence

A Table of Equivalence shall indicate differences and similarities in, at least, the following areas:

- mechanical (constructional) design of the mechanism responsible for the generation/regulation of the fluid flow (pumping mechanism);
- characteristics and design of sensors directly involved in sensing the fluid path, e.g. pressure sensors, drip sensors, air sensors;
- specific administration sets or single use sets recommended for use with the device;
- design and characteristics of the mains AC power supply;
- type and characteristics of internal power supply/s and re-charging regime if applicable;
- available units/mode of dosage, e.g. volume (mL)(mg) , flow (mL/hr)
- all available output ranges, e.g. 1 mL/hr to 1000 mL/hr;
- all available functions, e.g. continuous delivery, bolus delivery, secondary infusion, etc.;
- all available modes, e.g. general infusion, anaesthesia mode, PCA mode;
- access protection to different levels of programming, e.g. the use of PIN numbers for enabling keyboards, access to device reconfiguration limited to technical personnel only;
- implemented alarm conditions;
- characteristics of audible alarms and visual alarms; and
- whether the device is for use with specific drugs/substances.

Commercial and Regulatory History

Refer to Chapter 2.1 Information Applicable to all Registrable Therapeutic Devices.

Good Manufacturing Practice (GMP)

The Principal Manufacturer for the infusion device shall provide evidence of GMP for non-sterile manufacturing. The Principal Manufacturer for the sterile single use accessories shall provide acceptable evidence of GMP for sterile manufacturing. Refer to Chapter 1.19*Good Manufacturing Practice.*

Reporting Conditions

Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance

Refer to Chapter 1.6 *Postmarket Compliance Programs*.

Samples

If requested, the sponsor will supply on loan to the TGA, in the original packaging:

- 1 (one) sample of the device with any accessories needed for its operation, and
- 3 (three) samples of each consumable (e.g. infusion set, syringe, cassette) recommended for use with the device.

Any specific therapeutic claim in respect to the use of specific drugs in conjunction with the device may be subjected to evaluation by the Drug Evaluation & Safety Branch (DSEB) of the TGA.

Design / Materials / Testing

Design and Construction

The sponsor shall provide a description of the device including:

- a list of all performance characteristics and device specifications including but not limited to:
  - a statement of accuracy of the delivered flow or dose and an indication of the range of flow, and the volume for which this accuracy is applicable*;
  - maximum patient line pressures and associated alarms;
  - low battery warnings and associated alarms;
  - details on the method for air emboli detection/prevention;
  - any limits to the delivered volume or flow to prevent over-infusion;
  - delay times for the establishment of the desired flow rate following the start;
  - delay times for the occlusion/over-pressure detection to alarm;
  - the maximum volume of fluid that can be delivered to the patient on releasing an occlusion;
  - the recommended change interval (maximum working life in hours) for any single use products, e.g. administration set, etc.;
- design philosophy and principle of operation;
- dimensions of the assembled device, its components and accessories;
- description and general block diagram of any resident software; and
- details on any communication port allowing communication between the infusion device and an external computer system;
- mechanical drawings showing any mechanism involved in controlling/regulating the rate of infusion or dosage; and
- indication or specification of the capability of the device to resist ingress of fluids, and to resist impacts and other forces, if such factors can affect the safety and effectiveness of the device.

*for flow rates equal to and over 1 mL/hr the requirements in IEC601-2-24 Standard apply.

For the administration sets, the sponsor shall also provide:

- a drawing of the set, and
- the physical characteristics relevant to the part of the set responsible for the control of the flow, or any sensing on the fluid path which is critical to the safety and effectiveness of the pump-set system.

Computer Control

For infusion devices where control from an external computer is possible,

- computer hardware and software in personal computers where therapeutic applications are claimed, will be regulated within the existing regulatory framework.
- separate entry will be made in the ARTG, in accordance with the *Therapeutic Goods Regulations*, under the *Therapeutic Goods Act 1989*, for:
  - the proprietary hardware/software platform, with conditions that stipulate that the relevant applicable requirements in the suite of electrical medical equipment standards AS3200.1 (equivalent to IEC601-1 or EN60601-1) are met when the proprietary hardware is operated within a host computer;
  - each compiled software module that implements a function for a particular medical application and falls under the definition of a separate and distinct product;

- in addition to the requirements, and as a condition of supply of the proprietary hardware/software platform and/or the compiled software module, the supplier must place labelling, Product Information or product literature, in the product where appropriate:
  - warnings on the restrictions of use;
  - specific or unique hardware and software requirements including compatibilities and incompatibilities;
- a version control identifier must be placed on each product that is entered in the ARTG and this shall be easily accessed by the user.

Materials

If any material in the device is critical to the safety and effectiveness of the infusion (e.g. a spring in the pumping mechanism on which the accuracy of the dosage depends), a description, specifications and source of such material must be provided.

Labelling

For the pump, single use accessories and the packaging of single use accessories, copies of the labelling as it will be supplied in Australia shall be included. The labelling/product information of pump administration sets shall clearly state the device with which the set is recommended to work and the recommended change period of the set.

Packaging

Description of the packaging for sterile single use accessories, like administration sets, shall be included in the submission.

Product Information / Instructions for Use / Promotional Material

All literature (or copies of it) provided with, or used in the marketing of, the device must be included in the submission. This includes, but is not limited to:

- user manual,
- operator's manual,
- quick reference charts.

If any of the above information is not supplied, justification is required for these decisions or the application will be considered for rejection.

Sponsors are responsible for ensuring that any Product Information supplied separately from the product, for whatever intended purpose, is entirely consistent with the information supplied with the product and approved during evaluation, and that additional claims are not made.

Testing — Qualification Testing — Verification

The sponsor shall submit results of any studies on functional aspects of the device to verify the device specifications, with details of test methods used. Verification should be conducted in accordance with the International standard IEC-601-2-24 *Particular Requirements for Infusion Pumps and Controllers.*

Electrical Safety Testing

The sponsor shall provide certificates and test reports (checklists) or equivalent evidence that the device complies with the relevant electrical safety standards for a medium risk device, as indicated in Chapter 1.17 *Electrical Safety.*

Electromagnetic Compatibility

The sponsor shall provide a Report and copies of any Certification showing that the device meets the published electromagnetic compatibility (EMC) standard AS/NZS 3200.1.2 or IEC 601-1-2. The level of immunity against electromagnetic radiation (EMI) and the test voltage levels for electrostatic discharge (ESD) shall be those specified in the IEC-601-2-24 Standard.

Human Clinical Data

In particular circumstances, Human Clinical Data may be requested by the TGA.

Ch. 2.12 Drug Infusion Systems (Powered, Non Implantable)

Please include this completed checklist with your submission

A tick ✓ indicates information that is to be supplied as part of the submission

Fee Structure	Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.12	Reference Vol/Page
	General Details	✓		/
	Risk Analysis	✓		/
	Table of Equivalence #	✓	✓	/
	Commercial and Regulatory History	✓		/
	GMP	✓	✓	/
	Reporting Conditions	✓		/
	Postmarket Surveillance	✓		/
	Samples	✓	*	/
	Quarantine ##	✓		/
Design/	Design and Construction	✓	✓	/
Materials/	Materials	✓	✓	/
	Labelling	✓	✓	/
	Packaging	✓	✓	/
	Product Info/Instr for Use/Promo Material	✓	✓	/
Testing	Testing	✓	✓	/
Manufacturing/	Manufacturing	✓		/
Quality Control/	Quality Control	✓		/
Sterility	Sterility	✓		/
Biocompatibility/	Biological Safety/Biocompatibility Testing	✓		/
Preclinical (in vivo)	Preclinical (in vivo)	✓		/
Human Clinical Data	Human Clinical Data	*		/

\# to be provided if equivalence to a predicate device is being claimed,

should comply with AQIS requirements for imported devices containing human and animal derived material

* May be requested by the TGA during the evaluation process

Ch. 2.12 Drug Infusion Systems (Powered, Non Implantable) — Table of Equivalence

If Equivalence is being sought for a reduction in evaluation fees
*please include this **completed** Table of Equivalence with your submission*

Please indicate ✓ where *Predicate* and *Equivalent* Information is supplied, and reference details within the submission

Fee Structure	Evaluation Categories	✓ Registered Predicate Device	✓ Equivalent Information New Device	Reference Vol/Page
Design/	Design and Construction	_____	_____	/
Materials/	Materials	_____	_____	/
	Labelling	_____	_____	/
	Packaging	_____	_____	/
	PI/Instructions for Use/PM #	_____	_____	/
Testing	N/A			
Manufacturing/ **Quality Control/** **Sterility**	N/A N/A N/A			
Biocompatibility/ **Preclinical (in vivo)**	N/A N/A			
Human Clinical Data	Human Clinical Data			

Product Information/Instructions for Use/Promotional Material

2.13 EXTRACORPOREAL THERAPY SYSTEMS

Extracorporeal therapy systems which contain tissues, cell lines or substances derived from human or animal sources, or are used as components within a system to separate, purify or maintain a body fluid or tissue *ex vivo* prior to infusion, transfusion, implantation or transplantation, are classified as registrable therapeutic goods.

If the only animal material used within the good is included in the list in this box, the Extracorporeal System may be listable (refer to Chapter 3.3 *Animal Derivatives Contained in Listed Devices* or contact the Medical Devices Section, TGA, for advice):

animal derived waxes; or
heparin, unless heparin is being delivered as a drug; or
sintered hydroxyapatite; or
gelatin that conforms to generally accepted pharmacopoeial standards.

Additional requirements are specified in either Chapter 2.10 *Animal Origin Devices*, or, for human derived components, Chapter 2.15 *Human Origin Devices*.

Each registrable device submission must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

General Details
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Risk Analysis
Refer to Chapter 2.5 *Risk Analysis.*

Table of Equivalence
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Commercial and Regulatory History
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice
Refer to Chapter 1.19 *Good Manufacturing Practice.*

Reporting Conditions
Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance
Refer to Chapter 1.6 *Postmarket Compliance Programs.*

Samples
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Design / Materials / Testing

Design / Construction
For extracorporeal therapy goods/systems which comprise hardware/software components, the sponsor must:

- demonstrate a controlled development life cycle for the product;
- show the test plan and the results of tests.

Relevant equipment safety standards should also be met, refer to Chapter 1.17*Electrical Safety.*

Labelling
If the system consists of a number of separate goods, the submission shall include labels or compliance plates for each item. Refer to TGO 37*Requirements for the Labelling of Therapeutic Devices* (see Appendix 16).

Manufacturing / Quality Control / Sterility

Sterility
If the system consists of a number of separately packagedand sterilized goods, the appropriate points of the Sterility issues should be addressed for each. Refer to Chapter 2.6*Sterility*, and Appendix 15, *Standard for Sterile Therapeutic Devices*.

Biocompatibility / Preclinical

Biological Safety and Biocompatibility Testing
Biological safety should be demonstrated for the components of the extracorporeal product or system that come into contact with the autograft or allograft tissues during the therapy. If any part(s) of the product/system is commonly used in association with other procedures and is subjected to the same chemicals and the same physical treatment, equivalence with these procedures may be claimed; for example, blood collection bags. Refer to Chapter 2.7 *Biological Safety and Biocompatibility Testing*.

Human Clinical Data

Extracorporeal Therapies containing Monoclonal Antibodies

For guidance on specific clinical data requirements aimed at monoclonal antibody components of a therapy, sponsors should refer to the *Guidelines on Clinical Data to Support Applications for Monoclonal Antibodies,* published in the *Australian Guidelines for the Registration of Drugs Vol. 1, July 1994*, available from the TGA Publications Office.

Other Therapies

If other therapy regimes are used, reference should be made to Chapter 2.8 *Human Clinical Data.*

Ch. 2.13 Extracorporeal Therapy Systems*Please include this completed checklist with your submission*
A tick ✓ indicates information that is to be supplied as part of the submission

Fee Structure	Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.13	Reference Vol/Page
	General Details	✓	✓	/
	Risk Analysis	✓		/
	Table of Equivalence #	✓		/
	Commercial and Regulatory History	✓		/
	GMP	✓		/
	Reporting Conditions	✓		/
	Postmarket Surveillance	✓		/
	Samples	✓		/
	Quarantine ##	✓		/
Design/	Design and Construction	✓	✓	/
Materials/	Materials	✓		/
	Labelling	✓	✓	/
	Packaging	✓		/
	PI/Instructions for Use/PM **	✓		/
				/
Testing	Testing	✓		
Manufacturing/	Manufacturing	✓		/
Quality Control/	Quality Control	✓		/
Sterility	Sterility	✓	✓	/
Biocompatibility/	Biological Safety/Biocompatibility Testing	✓	✓	/
Preclinical (in vivo)	Preclinical (in vivo)	✓		/
Human Clinical Data	Human Clinical Data	✓	✓	/

\# to be provided if equivalence to a predicate device is being claimed
should comply with AQIS requirements for imported devices containing human and animal derived material
** Product Information/Instructions for Use/Promotional Material

Ch. 2.13 Extracorporeal Therapy Systems — Table of Equivalence

If Equivalence is being sought for a reduction in evaluation fees
*please include this **completed** Table of Equivalence with your submission*

Please indicate ✓ where *Predicate* and *Equivalent* Information is supplied, and reference details within the submission

Fee Structure	Evaluation Categories	✓ Registered Predicate Device	✓ Equivalent Information New Device	Reference Vol/Page
Design/	Design and Construction	_____	_____	/
Materials/	Materials	_____	_____	/
	Labelling	_____	_____	/
	Packaging	_____	_____	/
	PI/Instructions for Use/PM**	_____	_____	/
Testing	N/A			
Manufacturing/	Manufacturing	_____	_____	/
Quality Control/	Quality Control	_____	_____	/
Sterility	Sterility	_____	_____	/
Biocompatibility/	Biological Safety/Biocompatibility Testing	_____	_____	/
Preclinical (in vivo)	Preclinical (in vivo)	_____	_____	/
Human Clinical Data	Human Clinical Data			/

** Product Information/Instructions for Use/Promotional Material

2.14 HEART VALVE PROSTHESES

To assist with global harmonisation for medical device regulatory agencies, the TGA requirements for heart valve prostheses referred to in this section are based on documentation from the Food and Drug Administration of the US Department of Health and Human Services and the international standard ISO 5840:1996 *Cardiovascular implants — Cardiac valve prostheses*.

Each registrable device submission must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

General Details

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*.

Risk Analysis

Refer to Chapter 2.5 *Risk Analysis*.

Table of Equivalence

A Table of Equivalence must indicate the differences and similarities in the following:

- for mechanical prosthetic heart valves:
  - the materials used in the valve,
  - the design of the valve,
  - assembly technique,
  - testing and quality control procedures,
  - haemodynamic properties,
  - packaging and sterilization procedures;
- for biological prosthetic heart valves:
  - the materials used in the valve,
  - the design of the valve,
  - assembly technique(s),
  - testing and quality control procedures,
  - haemodynamic properties,
  - tissue preservation and/or cross-linking technique(s),
  - anticalcification treatment(s),
  - packaging and sterilization procedures.

An example of a Table of Equivalence is shown at the end of this chapter.
Refer also to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*.

Commercial and Regulatory History

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice (GMP)

The sponsor of a prosthetic heart valve (PHV) shall provide evidence of GMP for manufacturing of the prosthetic heart valve, acceptable to the GMPAL Section of TGA. Refer to Chapter 1.19 *Good Manufacturing Practice.*

For prosthetic heart valves, both the Principal and Alternative Manufacturing sites are defined as the site where the following manufacturing steps are performed:

- manufacture of the components (occluder/leaflets, orifice, struts, stents, sewing cuff); for definitions of terms that can be used to identify the heart valve substitute components, refer to ISO 5840:1996(E) *Cardiovascular implants — Cardiac valve prostheses, Annex E*;
- manufacture of elements to attach the sewing cuff to the orifice, etc.;
- assembly of the valve;
- packaging; and
- sterilization.

Reporting Conditions

In the submission, the sponsor shall:

- address the issue of device marking to enable identification in situ;
- provide details of procedures for maintaining a database of patient and device identification;
- provide details of the procedures for reporting and analysing problems with the device.

Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance

Following an independent assessment of the data submitted, the TGA may recommend the registration of a prosthetic heart valve, subject both to the standard conditions applying to registered therapeutic devices, and to additional conditions applying to registered therapeutic devices that are aimed at ensuring rigorous postmarket surveillance, as outlined below. If the sponsor fails to comply with these conditions, TGA may cancel the registration of the product.

a. The sponsor must maintain a register containing the names (or identifiers) of all heart valve recipients and treating physicians. The minimum data set for the register shall include the manufacturer and sponsor identifier(s), device model and catalogue numbers, type and size of the valve, device serial and batch number, patient identifier, hospital identifier, physician identifier, and procedure date. The register must be available for audit by the TGA.

b The sponsor must report, to the Director, Conformity Assessment Branch, TGA, all major adverse events (death and serious injury) related to heart valves reported to the manufacturer or sponsor, as soon as possible in all cases and within fourteen days. (It is recommended that the FDA*Draft Replacement Heart Valve Guidance, Appendix L, October 1994* be a reference for classification of adverse events.)

c. The sponsor must submit yearly, for a minimum of ten years, a detailed cumulative report to the Director, Conformity Assessment Branch, TGA, including the following information:
   i. the number of patients on register;
   ii. the number of deaths, including causes;
   iii. all adverse events associated with valves;
   iv. the patients lost to follow-up;
   v. a summary of overseas experience with the particular valve;
   vi. all papers published in relation to the valve since the last reporting period;
   vii. a cumulative statistical analysis of the performance of the valve.

   Notes:
   1. The data should be collected with the input of the referring physicians.
   2. Patients lost to follow-up after all avenues are exhausted will be included as an adverse outcome. The *National Death Index* compiled by the Australian Institute of Health and Welfare (AIHW) is a possible source to be used by the referring physician or surgeon. If the name is found, the cause of death should be checked on the death certificate and confirmed by review of hospital records if possible.

d. All patients enrolled in Australian clinical trials (CTN, CTE) or receiving prosthetic heart valves under IPU prior to the registration of the valve are to be placed on the implant register maintained by the sponsor and included in any reports or analyses of the performance of the valve.

Refer also to Chapter 1.6 *Postmarket Compliance Programs.*

Samples

Samples of the packaging material, including sterile trays and external package, must be included in the submission.

Design / Materials / Testing

Design — Additional Requirements

A brief description of the device is required, including a summary of the engineering and/or scientific considerations in relation to the design specifications.
For **new and predicate** prosthetic heart valves, the following are required:

- drawings, including dimensional specifications for each valve size, showing components and accessories;
- for mechanical heart valves, a full stress analyses of all implanted components;
- fixation and implantation techniques;
- the maximum level of noise created by the valve;
- the type and amount of distortion of the natural flow field;
- the sewing ring configuration;
- details of the sewing ring material.

The submission should also contain the rationale used to establish and optimise key design features of the valve, including, but not limited to, the:

- haemodynamic function;
- occluder geometry and kinematics;
- choice of materials; and
- structural configuration.

For mechanical valves, this description must also include a discussion of the opening angle. For tilting disc valves, information on the optimisation of disc curvature and eccentricity (the ratio of the displacement of the pivot axis from the valve centre to the occluder diameter) may be appropriate. This discussion should focus on the fact that literature reports have shown that optimising these quantities is essential in controlling the opening torque, flutter, pressure losses across the valve, and flow characteristics.

Materials — Component Materials

A complete listing of all materials used in the fabrication or processing of the heart valve, including their generic chemical names or biological sources, must be provided. All fabrication processes used for all constituent materials in both the raw material and finished product form must also be specified.

All components used in the heart valve must be described. The physical and chemical characteristics and allowable tolerances of these components must be tested according to:

- ISO 5840:1996(E) *Cardiovascular implants — Cardiac valve prostheses*: Table 1 'Physical and chemical properties for evaluation of heart valve substitute components',
  Table 2 'Physical and chemical properties for application to design of heart valve substitutes and their components',
- Annexes C, D and E of that standard.

Packaging — Shelf Life and Storage Conditions

- The protocol for shelf life studies must include the effects of temperature, humidity, pressure and light exposure as well as shipping and handling.
- After subjecting the assemblies to the simulated environment, the devices must be tested for sterility and functionality.
- For tissue valves, the shrink temperature, moisture content, collagen content, percentage and volume of remaining preservative ingredients, leakage, seal integrity and other appropriate tests must be performed.

Product Information / Instructions for Use / Promotional Material

All literature provided with, or used in the marketing of the device must be provided with the submission. This includes, but is not limited to:

- Physician's Manuals and Implanting Instructions;
- copies of any information provided separately to clinical staff, including training or instructional literature, video cassettes, movies or visual aid materials and warnings;
- Copies of any information provided separately to patients, including warnings and cautions;
- copies of any promotional or advertising material concerning the device, components and accessories;
- any set of forms used in tracking the device (e.g. patient registration forms).

Testing – Mechanical Testing & Analysis

All testing must be performed on valves which are produced using the final design and manufacturing specifications. Test samples should be sterilized by the process to be used for production purposes. Furthermore, before conducting in vitro testing, the valve must be subjected to the maximum number of re-sterilization cycles using the worst-case method and/or conditions specified for use with the valve. If necessary, removal of the sewing ring prior to testing is acceptable.

For recommended methods for testing of **stentless** biological prosthetic heart valves, refer to *Replacement Heart Valve Guidance, US Department of Health and Human Services, Food and Drug Administration, Division of Cardiovascular, Respiratory, and Neurological Devices, October 14, 1994.*

Hydrodynamic Testing

The following data shall be provided for both new and predicate devices with appropriate comments:

- steady forward-flow testing,
  - test and the test equiment must conform to ISO 5840:1996(E) *Cardiovascular implants — Cardiac valve prostheses*;
- steady back-flow leakage testing,
  - test and the test equipment must conform to ISO 5840:1996(E) *Cardiovascular implants — Cardiac valve prostheses*;
- pulsatile-flow testing,
  - test and the test equipment must conform to ISO 5840:1996(E) *Cardiovascular implants — Cardiac valve prostheses*;
- flow visualization,
  - refer to *Replacement Heart Valve Guidance, US Department of Health and Human Services, Food and Drug Administration, Division of Cardiovascular, Respiratory, and Neurological Devices, October 14, 1994*;
- cavitation potential (not required for biological prosthetic heart valves),
  - refer to *Replacement Heart Valve Guidance, US Department of Health and Human Services, Food and Drug Administration, Division of Cardiovascular, Respiratory, and Neurological Devices, October 14, 1994;*
- verification of the Bernoulli relationship,

- refer to *Replacement Heart Valve Guidance, US Department of Health and Human Services, Food and Drug Administration, Division of Cardiovascular, Respiratory, and Neurological Devices, October 14, 1994*.

Durability Testing

Durability tests and the test equipment should be as specified in ISO 5840:1996(E) *Cardiovascular implants — Cardiac valve prostheses*, and the reports shall be supplied in the submission.

Hydrostatic Testing

Provide details of the following:

- Hydrostatic Failure Mode; Static Pressure; 'Burst Test'
  - hydrostatic test data that indicate the minimum applied load that results in permanent deformation and/or fracture of the occluder(s) or any support structure, as recommended by ISO 5840:1996(E) *Cardiovascular implants — Cardiac valve prostheses*, C.5.4.

Dynamic Failure Mode

Pulsatile test data that indicate the qualitative and/or quantitative assessment of the failure modes and high stress areas in the valve must be provided. For detailed information on how to conduct this test, refer to *Replacement Heart Valve Guidance, US Department of Health and Human Services, Food and Drug Administration, Division of Cardiovascular, Respiratory, and Neurological Devices, October 14, 1994.*

Sewing Ring Push-off

Three valves of each size and each type should be tested, and the results reported in the submission. Maximum loads which can be supported by the valve, and a comparison to physiological loading, as recommended by ISO 5840:1996(E) *Cardiovascular implants — Cardiac valve prostheses*, C.5.6, must be determined.

Design Specific Testing

If appropriate, data shall be provided on the

- creep of stents for stented bioprosthetic valves,
- deflection of stents for stented bioprosthetic valves,
- ball ejection force for ball-and-cage mechanical valves,
- leaflet impingement force for bileaflet valves,
- leaflet escape force for bileaflet valves,
- sewing ring torque,
- absorption and adsorption in polymeric materials,
- corrosion for metallic valves.

For detailed information on how to conduct the above tests, refer to *Replacement Heart Valve Guidance, US Department of Health and Human Services, Food and Drug Administration, Division of Cardiovascular, Respiratory, and Neurological Devices, October 14, 1994*.

Stress Analysis

A thorough stress analysis of the valve and its structural components should be completed. (For the stentless valve this analysis is not required.) This analysis should include:

- computer modelling of the maximum stress to which part of the prosthetic heart valve will be subjected. This method should take into consideration the peak loads that are expected, including dynamic effects;
- static stresses;
- dynamic stresses;
- residual stresses; and
- stress concentrations.

In particular, it should at least include:

- measurement of worst case physiological loads or deflections that are applied to the valve components;
- a static finite element analysis (FEA), or equivalent, that identifies the stress distribution in the valve components, including the magnitude and location of the maximum static stress;
- a determination of the areas and/or components of the valves which are critical structural areas;
- the addition of the residual stresses which are present from manufacturing and/or production to the static stresses;
- for mechanical valves, the determination of the magnitude and locations of the transient loads present at valve opening or closing, whichever is worse.

This analysis should be performed on the valve which experiences the highest stresses (proof of that should also be provided).

For detailed information on this requirement, refer to *Replacement Heart Valve Guidance, US Department of Health and Human Services, Food and Drug Administration, Division of Cardiovascular, Respiratory, and Neurological Devices, October 14, 1994* and/or contact the TGA.

Component Fatigue Lifetime Determination

The likelihood that any non-biological structural components (excluding sewing rings) in the prosthetic valve (e.g. struts, stents, housings and leaflets) will fail by fatigue within 380 x 10^6 cycles when subjected to physiological loading parameters, must be determined. In addition the physiological loading parameters must be stated and justified.

A conservative fatigue analysis of these components must include the following:

- S/N endurance limit:
  - provide statistically valid data to determine the fatigue strength for the material at 380 x 10^6 cycles when subjected to physiological loading parameters;
- damage tolerance analysis for metal and ceramic components:
  - fracture toughness of the material;
  - the crack growth rate for an appropriate load ratio (cyclic and sustained loading) and physiological environment;
  - critical crack size which will not propagate to failure in 380 x 10^6 cycles;

- calculation of the minimum assured lifetime of the valve in a continuously hypertensive patient;

- fatigue properties and manufacturing processes.

The submission should discuss the effect of the following manufacturing issues, as applicable, on the anticipated life of the valve:

- the presence of voids or impurities in as-received materials;
- the presence of voids or impurities introduced during a manufacturing process;
- the accuracy of methods used to ensure that the sizes of the cracks present in the material are below critical crack length;
- the effects of the dimensional changes imposed on the valve components during assembly, and a determination of the resulting stresses in the valve;
- low cycle fatigue;
- the effects of in-tolerance variations in clearances on the magnitude of the deformation of components required to assemble the valve.

Valved Conduits

If both the valve and the graft have previously been approved for marketing, the validation of the new design must include, at a minimum, in vitro studies which clearly establish that the valve/graft interface can withstand physiological loading. If a coated graft is used, in vitro studies should be conducted to determine if the manufacturing steps associated with the sewing of the valve into the graft have adversely affected the coating, and subsequently the bleeding at implant.

Manufacturing / Quality Control / Sterility

Manufacturing Process

Details of the manufacturing processes for a Prosthetic Heart Valve must be provided, including further details on site interfaces (transfer of products or components from one site to a different site). Details of any subassemblies provided by third party manufacturers are required. The submission should detail any manufacturing/clinical/assembly concerns for the sewing cuffs and the leaflets.

For components made of **pyrolytic carbon**, the relevant properties referenced in ISO 5840:1996(E) *Cardiovascular implants — Cardiac valve prostheses*, Table 1 'Physical and chemical properties for evaluation of heart valve substitute components', and Table 2 'Physical and chemical properties for application to design of heart valve substitutes and their components', and in annexes C, D and E of that standard, must be measured and the test data supplied in the sponsor's submission. The manufacturer should determine the most suitable test methods for obtaining this information, and demonstrate that the particular test method chosen will measure the desired property with sufficient sensitivity. To ensure that the reported properties are truly representative of the manufacturing process, the values reported should be measured directly on manufactured parts and not cited from the literature. Evidence should also be provided that the coating temperature and coating rate are sufficiently controlled to ensure that residual stresses for each component remain within specification and that the occurrence of internal cracks, voids, etc., are minimised.

The sizing method used in the manufacturing process must be described in detail.

The submission must include a detailed description of the assembly process. For mechanical valves, details of the procedure used to insert the occluder and/or leaflets into place must be provided. If in any stage a mechanical or thermal stress is induced in a component or in the whole prosthetic heart valve, a detailed description of this stage is required.

The submission must include a flow chart with full details of each major step in the manufacturing process. If the manufacture is carried out at different sites, the chart must indicate this and details must be provided on any control on the transferred subassemblies.

For **biological** prosthetic heart valves, the submission must describe tissue fixation parameters, and acceptance criteria for valves as received from the slaughter house. These acceptance criteria must include not only the maximum allowable size for fenestrations, tears, and tissue peel, but also a maximum allowable number of defects per valve, as well as critical locations which must not contain defects.

For the relevant material and design characteristics as specified in

- ISO 5840:1996(E) *Cardiovascular implants — Cardiac valve prostheses*,
  Table 1 'Physical and chemical properties for evaluation of heart valve substitute components',
  Table 2 'Physical and chemical properties for application to design of heart valve substitute and their components',
- Annexes C, D and E of that standard,

indicate which parameters are routinely measured as part of the manufacturing quality assurance program.

Sponsors of **biological prosthetic heart valves** should refer to Chapter 2.10 *Animal Origin Devices* for the additional requirements to be provided in a submission for registration of animal-derived devices.

Sterility

Details on the sterilization process for the device and its implication on the device's clinical performance, safety and biocompatibility are required. Criteria for the disposal and re-sterilization of devices for which sterility have been compromised are also required.

Where specific cleaning and/or disinfection solutions or accessories are required for the device, descriptions of containers, composition of solutions, any equipment required and their specifications are required.

Refer also to Chapter 2.6 *Sterility*

Biocompatibility / Preclinical Biological Safety and Biocompatibility Studies

Refer to Chapter 2.7 *Biological Safety and Biocompatibility Testing.*

Preclinical *in vivo* Studies

Preclinical studies should be performed and documented as recommended in the Standard ISO 5840 (November 1996) *Cardiovascular implants — Cardiac valve prostheses*.

Anticalcification Treatment Studies *Biological Prosthetic Heart Valves*

For bioprosthetic valves, anticalcification treatment studies must be designed to evaluate the effectiveness of proprietary treatments designed to mitigate calcification. These studies are required only if the tissue is treated with an anticalcification treatment. The effectiveness of the treatment must be demonstrated in an appropriate chronic animal model. Validation of the animal model (species, age, implantation site, animal housing) must include the demonstration of bioprosthetic valve calcification. It may be possible to validate the use of a non-orthotopic implantation site for the purpose of collecting data. These studies must include a quantitative comparison of the extent of calcification in a treated valve versus an untreated control valve of identical design and fabrication. A statistically significant difference between treated and control valves should be demonstrated. Animal data alone are not considered sufficient to support claims of anticalcification treatment efficacy.

Accessories

The following information must be provided for accessories to heart valves:

- the intended use,
- the labelling and instruction for use,
- the sizes in which in which any accessory(ies) are available,
- the type of valve with which the accessories should be used,
- material(s) from which they are fabricated,
- a description of manufacturing methods,
- a description of biocompatibility testing or historical use of the material(s),
- dimensional drawings,
- the number of times the accessory(ies) can be used,
- the sterility state,
- how many times the accessory(ies) can be resterilized, and if the recommended number of resterilizations is based on testing or historical data,
- how the accessory is supplied (e.g. as a kit, individually, etc.),
- packaging,
- if any accessory is supplied non-sterile, the instructions for use must contain recommended sterilization cycles. These cycles must be validated.

Refer to *Replacement Heart Valve Guidance, US Department of Health and Human Services, Food and Drug Administration, Division of Cardiovascular, Respiratory, and Neurological Devices, October 14, 1994.*

Human Clinical Data

Human clinical data should be presented in accordance with Chapter 2.8 *Human Clinical Data*. In addition, the clinical evaluation of heart valves should be performed, documented and reported as recommended in the Standard, ISO 5840 (November 1997) *Cardiovascular implants — Cardiac valve prostheses*.

These are additional requirements for stentless tissue heart valves:

a. the tissue stentless heart valves should only be used by clinicians trained in the implantation of the valve. Training may be through a sponsor-initiated program or through certification by a specialist professional group.

b. explanted stentless tissue heart valves should be returned for assessment to the manufacturer/sponsor and/or an independent authority;

c. deaths of recipients of stentless tissue prosthetic heart valves should be reviewed by a Clinical Panel or hospital equivalent (or another acceptable review process) where possible, to assess whether death was related to the failure of the prosthetic heart valve.

Reference documents

ISO 5840:1996(E) Cardiovascular implants — Cardiac valve prostheses.

DRAFT Replacement Heart Valve Guidance, US Department of Health and Human Services, Food and Drug Administration, Division of Cardiovascular, Respiratory, and Neurological Devices, October 14, 1994.

Ch. 2.14 Heart Valves

Please include this completed checklist with your submission

A tick ✓ indicates information that is to be supplied as part of the submission

Fee Structure	Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.14	Reference Vol/Page
	General Details	✓		/
	Risk Analysis	✓		/
	Table of Equivalence #	✓	✓	/
	Commercial and Regulatory History	✓		/
	GMP	✓	✓	/
	Reporting Conditions	✓	✓	/
	Postmarket Surveillance	✓	✓	/
	Samples	✓	✓	/
	Quarantine ##	✓		/
Design/	Design and Construction	✓	✓	/
Materials/	Materials	✓	✓	/
	Labelling	✓		/
	Packaging	✓	✓	/
	PI/Instructions for Use/PM **	✓	✓	/
Testing	Testing	✓	✓	/
Manufacturing/	Manufacturing	✓	✓	/
Quality Control/	Quality Control	✓		/
Sterility	Sterility	✓		/
Biocompatibility/	Biological Safety/Biocompatibility Testing	✓		/
Preclinical (in vivo)	Preclinical (in vivo)	✓	✓	/
Human Clinical Data	Human Clinical Data	✓	✓	/

\# to be provided if equivalence to a predicate device is being claimed

should comply with AQIS requirements for imported devices containing human and animal derived material

** Product Information/Instructions for Use/Promotional Material

Ch. 2.14 Heart Valves — Table of Equivalence

If Equivalence is being sought for a reduction in evaluation fees
please include this completed Table of Equivalence with your submission

Please indicate✓ where *Predicate* and *Equivalent* Information is supplied, and reference details within the submission

Fee Structure	Evaluation Categories	✓ Registered Predicate Device	✓ Equivalent information New Device	Reference Vol/Page
Design/	Design and Construction	_____	_____	/
Materials/	Materials	_____	_____	/
	Labelling	_____	_____	/
	Packaging	_____	_____	/
	PI/Instructions for Use/PM	_____	_____	/
Testing	N/A			
Manufacturing/	Manufacturing	_____	_____	/
Quality Control/	Quality Control	_____	_____	/
Sterility	Sterility	_____	_____	/
Biocompatibility/	Biological Safety/Biocompatibility Testing	_____	_____	/
Preclinical (in vivo)	Preclinical (in vivo)	_____	_____	/
Human Clinical Data	Human Clinical Data			/

** Product Information/Instructions for Use/Promotional Material

2.15 HUMAN ORIGIN DEVICES

Sponsors are advised to contact the TGA before submitting an application if confirmation of submission requirements is needed. Reference should also be made to Appendix 11, *Human or Animal Origin Devices.* Devices made of or containing human tissue are classified into four separate categories based on the source of the material.

1 Commercial
Human tissue, commercially retrieved and processed for supply in Australia, must be registered in the ARTG.

2 Tissue Bank — 'Secondary Processed Tissue' (Tissue Engineered)
Human tissue, procured by a tissue bank or hospital, for implantation in or on the human body, that is processed by steps which **deliberately alter** the biological or mechanical properties of the tissue, must be registered in the ARTG, and the Tissue Bank must comply with the *Australian Code of Good Manufacturing Practice for Therapeutic Goods — Human Tissues*.

3 Tissue Bank — 'Primary Processed Tissue'
Human tissue, procured by a tissue bank or hospital, for implantation in or on the human body **without any deliberate alteration** to its biological or mechanical properties is **exempt from registration** in the ARTG, but the supplying Tissue Bank must comply with the *Australian Code of Good Manufacturing Practice for Therapeutic Goods — Human Tissues*.

4 Direct donor-to-recipient transplantation (without storage)
Fresh viable human tissue (other than blood), human organs, parts of organs, human bone marrow for direct donor-to-matched-recipient transplant are **not therapeutic goods** under Section 7 of the *Therapeutic Goods Act 1989* and are **exempt from registration** in the ARTG.

Applications For Registration of Categories 1 & 2 Sources of Human Tissue
An application for registration of a human-tissue-derived device, or a device component of human material, retrieved and processed by a tissue bank or commercial organisation must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

General Details

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Risk Analysis

Refer to Chapter 2.5 *Risk Analysis*.

Table of Equivalence

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Commercial and Regulatory History

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice

Prior to making an application to register products derived from human tissue, the TISSUE BANK or manufacturer must be audited to the *Australian Code of Good Manufacturing Practice for Therapeutic Goods — HUMAN TISSUES* or an approved Code under the *Therapeutic Goods (Manufacturing Principles*) *Determination No.1 of 1998*. To initiate this action the sponsor should forward

a completed *Application for a Licence to Manufacture Therapeutic Goods* form (available from the TGA Publications Office),
the application fee and
a letter requesting:

- an audit of the Tissue Bank and/or manufacturing site/s,
- the applicable Inspection fee, and
- an anticipated date for audit, or
- advice on an alternative approved Code,

to:

Head,
GMP Audit and Licensing Section (GMPALS)
Conformity Assessment Branch, TGA
MDP 122
PO Box 100
Woden ACT 2606

Refer to Chapter 1.19 *Good Manufacturing Practice.*

Reporting Conditions

Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance

For each batch of each component of human material of the therapeutic good, the sponsor must undertake to:

- keep records of distribution within Australia;
- ensure access to all donor records, so that products can be traced between donor/s and recipient/s; and
- ensure these records are retained and are available for inspection for a period of not less than 20 years.

Records held by the sponsor may be inspected by the TGA.

Samples

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Quarantine

For Imported Devices Only

Evidence of the issue of an Import Permit in accordance with the *Quarantine Act (1908)* must be provided. Compliance with the *Quarantine Act (1908)* is a function of the Australian Quarantine and Inspection Service (AQIS) of the Department of Primary Industries and Energy (DPIE). Sponsors are required to obtain an Import Permit for importation of human, animal or plant material. Refer to Chapter 1.4 *Quarantine Requirements (AQIS).*

Design / Materials / Testing

Labelling

The outer package label should make a statement indicating the device contains material of human origin. Refer also to Appendix 16, *TGO 37 Requirements for Labelling for Therapeutic Devices*.

Product Information / Instructions for Use / Promotional Material

The following statement, or one of similar intent, must be included in information provided separately to patients:

> 'This device is derived from human tissue and although care has been exercised in its manufacture to minimise the human pathogen content, a potential risk is present and absolute freedom of infective agents cannot be guaranteed'.

Manufacturing / Quality Control / Sterility

Refer to Chapter 2.6 *Sterilty*

Source Materials and Risk of Infectivity — Human Materials

If more than one type of human-derived material is used to manufacture this therapeutic good, complete a copy of this declaration for each type.

Definitions:

Primary processing retrieval, cleaning/washing, trimming, segmenting, sterilization, and transferral to storage solutions (if appropriate) and containers, of human material at a tissue bank complying with the *Australian Code of Good Manufacturing Practice for Therapeutic Goods: Human Tissues* or the *Australian Code of Good Manufacturing Practice for Therapeutic Goods: Blood and Blood Products*, whichever is relevant.

Secondary processing steps of manufacture additional to those outlined in Primary processing that alter the physical or biological properties of human material, such as freeze-drying, extraction, etc. Manufacturing facilities must comply with the *Australian Code of Good Manufacturing Practice for Therapeutic Goods: Human Tissues* or the *Australian Code of Good Manufacturing Practice for Therapeutic Goods: Blood and Blood Products* or, in some instances, with other Manufacturing Principles (MPs) as determined under the *Therapeutic Goods Act 1989.*

Donor Selection and Screening

If GMP has been determined under *Manufacturing Principles* other than the *Australian Code of Good Manufacturing Practice for Therapeutic Goods: Human Tissue* or *Blood and Blood Products*, the procedures for quality control in donor selection and exclusion criteria exercised in retrieval of the human material must comply with the relevant sections of the appropriate Code.

- The submission must discuss fully each point in the Sections of the above Code which address donor selection and donor exclusion criteria in relation to the product.
- If in vitro diagnostic reagents or kits are used in the screening of donors, the submission must provide details of the product/brand(s), the name(s) of the kit manufacturer(s) and the regulatory status of the kit in the country in question.

Processing

The following information, giving details relevant to the human material contained in the therapeutic good, including evidence of compliance to standards and monographs, etc., must be provided:

- the name and category of the tissue or organ (according to the Note for *Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products — CPMP/BWP/877/96*) used to manufacture the therapeutic good;

- the procedures used in tissue retrieval, including conditions available at the retrieval site, e.g. prevention of cross-contamination, cleaning and sterilization of instruments between cadavers and patients;
- If cadaveric serum is used in determining freedom from disease or pathogens, the test methods, including their validation, must be described.
- justification of the tissue pooling, if applicable, and methods of control used to aid tracking from finished product to donors or their medical histories;
- identification of the manufacturing steps intended to reduce or inactivate the infective titre of agents causing transmissible spongiform encephalopathy or other prion diseases, viral and microbiological contamination which may be pathogenic to humans. Documented validation of each procedure must be submitted to support its efficacy.
- the steps of manufacture, if any, that are undertaken to comply with the advice provided in the relevant Committee for Proprietary Medicinal Products (CPMP) guidelines (e.g. *Note for Guidance on Plasma Derived Medicinal Products — CPMP/BWP/269/95; Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses — CPMP/BWP/268/95; Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products — CPMP/BWP/877/96*);
- the methods used to clean and sterilize manufacturing equipment between production batches to ensure inactivation of possible infectious agents;
- an assurance that human-derived materials or components from any other source are not used and that the supplier(s) will not be changed without the approval of the TGA.

Information regarding the sterilization of the finished therapeutic good should be supplied with the 'Sterility' component of the submission.

Biocompatibility / Preclinical

Biological Safety and Biocompatibility Testing

The submission must provide specifications for:

- the raw materials, including evidence that the harvest of tissue occured within a time period of death relevant to the material (e.g. 24 hours for dura mater) and with sufficient temperature control to limit the effects of autolysis;
- the reagents and final product and the methods of determination for each. Include levels and nature of impurities associated with the initial and final steps of manufacture. Protocols for each critical production step in the tissue manufacture must also be provided.

Refer also to Chapter 2.7 *Biological Safety and Biocompatibility Testing.*

Stability Testing and Shelf Life

Detailed descriptions of the stability testing and rationale for determined shelf life are required.

Additional Requirements for Tissues of CNS or Ophthalmic Origin

Human materials derived from the brain, pituitary gland, spinal cord, dura mater and eye, pose an increased risk of transmitting fatal neurodegenerative disease, therefore the following data must be submitted for evaluation for the first five batches of a product to be supplied in Australia. Thereafter the sponsor must hold similar evidence for each subsequent batch for TGA inspection upon request.

For each donor contributing to the batch of material, copies of the following must be provided:

- the death certificate, signed by the appropriate medical practitioner, which specifies the cause of death;
- sufficient documentation to ensure the donor is free from disease, which could include the following:
  - a statement, signed by a qualified medical practitioner who treated the donor in his or her last illness, that the donor did not suffer from any disease which would make the donor's tissues undesirable for processing into prosthetic graft material; and
  - a neuropathology report which includes a study of representative sections of the donor's cerebral cortex and confirms that there was no evidence of disease which would render the tissue unsuitable for processing into prosthetic graft material; and
  - a declaration that the donor had not undergone neurosurgery between 1972 and 1989 which involved the replacement of dura with a dura mater allograft.

A statement must be provided from the manufacturer that the decontamination treatment to which the batch of material was subjected met all treatment specifications.

Product Information / Instructions for Use / Promotional Material

The first application to supply dura mater/ophthalmic tissue products must include a copy of all product literature for review. This material must include statements in the package insert, for the information of the medical practitioner, to the effect that:

- information from the US Center for Disease Control suggests that evidence of Creutzfeldt–Jakob disease is found in 1/10,000 autopsies;
- the inactivation procedures performed during the manufacturing process cannot be relied on to completely inactivate agents causing spongiform encephalopathies including Creutzfeldt–Jakob disease (CJD);
- the Commonwealth Department of Health and Family Services recommends that the use of dural grafts be restricted to indications where there is no satisfactory alternative.

Any other virus not tested for and not destroyed by the decontamination process must be listed.

Human Clinical Data

Refer to Chapter 2.8 *Human Clinical Data*

Ch. 2.15 Human Origin Devices

Please include this completed checklist with your submission

A tick ✓ indicates information that is to be supplied as part of the submission

Fee Structure	Evaluation Categories	General Information Requirements ReferCh.2.1	Additional Information Required Refer Ch.2.15	Reference Vol/Page
	General Details	✓		/
	Risk Analysis	✓		/
	Table of Equivalence #	✓		/
	Commercial and Regulatory History	✓		/
	GMP	✓	✓	/
	Reporting Conditions	✓		/
	Postmarket Surveillance	✓	✓	/
	Samples	✓		/
	Quarantine ##	✓	✓	/
Design/	Design and Construction			/
Materials/	Materials			/
	Labelling	✓	✓	/
	Packaging	✓		/
	PI/Instructions for Use/PM **	✓	✓ ✓ *(CNS)**	/
Testing	Testing			/
Manufacturing/	Manufacturing	✓	✓	/
Quality Control/	Quality Control	✓		/
Sterility	Sterility	✓		/
Biocompatibility/	Biological Safety/Biocompatibility Testing	✓	✓ ✓ *(CNS)**	/
Preclinical (in vivo)	Preclinical (in vivo)	✓		/
Human Clinical Data	Human Clinical Data	✓		/

* additional information required for devices of CNS or Ophthalmic origin,

should comply with AQIS requirements for imported devices containing human and animal derived material

** Product Information/Instructions for Use/Promotional Material

Ch.2.15 Human Origin Devices — Table of Equivalence

If Equivalence is being sought for a reduction in evaluation fees
*please include this **completed** Table of Equivalence with your submission*

Please indicate ✓ where *Predicate* and *Equivalent* Information is supplied, and reference details within the submission

Fee Structure	Evaluation Categories	✓ Registered Predicate Device	✓ Equivalent information New Device	Reference Vol/Page
Design/	Design and Construction	_____	_____	/
Materials/	Materials	_____	_____	/
	Labelling	_____	_____	/
	Packaging	_____	_____	/
	PI/Instructions for Use/PM**	_____	_____	/
Testing	N/A			
Manufacturing/	Manufacturing	_____	_____	/
Quality Control/	Quality Control	_____	_____	/
Sterility	Sterility	_____	_____	/
Manufacturing/	Manufacturing	_____	_____	/
Quality Control/	Quality Control	_____	_____	/
Sterility	Sterility	_____	_____	/
Biocompatibility/	Biological Safety/Biocompatibility Testing	_____	_____	/
Preclinical (in vivo)	Preclinical (in vivo)	_____	_____	/
Human Clinical Data	Human Clinical Data			/

** Product Information/Instructions for Use/Promotional Material

2.16 INTRAOCULAR LENSES (IOL) — REGISTRABLE

Schedule 3 of the *Therapeutic Goods Regulations* states that implantable intraocular lenses, other than lenses that are included in item 13 or 14 of Part 1 of Schedule 4, are required to be registered.

Each registrable device submission must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

General Details

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Risk Analysis

Refer to Chapter 2.5 *Risk Analysis*.

Table of Equivalence

A Table of Equivalence must indicate the differences and similarities between the device and a predicate device in, at least, the following areas:

- specific sterile accessories or disposable sterile accessories that are recommended for use with the lens;
- the details of intended placement and method of fixation of the lens;
- manufacturing processes;
- the main steps in the manufacturing process;
- manufacturing sites.

Equivalence of the biocompatibility or biological safety characteristics of an IOL can be claimed when:

- the IOL materials, including surface modifications, are identical to a currently registered IOL; and
- the IOL materials, including surface modifications, are subjected to the same raw material processing as a currently registered IOL; and
- the IOL is subjected to the same manufacturing process, at the same manufacturing sites, as a currently registered IOL.

If a sponsor does not provide the necessary information to comply with any of the above requirements, it is their responsibility to justify why this information is not required. Refer to Chapter 2.3 *Equivalence/ Abridged Submissions.*

Commercial and Regulatory History
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice
Refer to Chapter 1.19 *Good Manufacturing Practice.*

Reporting Conditions
Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance
Refer to Chapter 1.6 *Postmarket Compliance Programs.*

Samples
One sample of the device in the original packaging, with any accessories needed for its implant, is to be supplied to TGA.

Design / Materials / Testing

Design / Construction
A description of the IOL, including but not limited to the following, is required:

- the basic design, e.g. monofocal, biconvex, 3 piece, UV absorbing, J-loop haptic;
- the overall diameter, optic diameter, dioptric power range, manufacturing technique;
- the optic & haptic material;
- the method of fixation;
- any indications & contraindications for use;
- any other information specific to the submitted IOL;
- details on parts of the device which are critical to the implant.

Information on the physical properties is required for all IOLs that:

- incorporate an IOL design radically different to that of any currently registered IOL; or
- are intended to be fixed in a position other than the posterior chamber; or
- are made from a material different to that of any currently registered IOLs; or
- are manufactured by a process significantly different to that of any currently registered IOLs; or
- incorporate any change in the manufacturing process, technological characteristics or intended use that may affect the physical properties of the material.

The following are examples of physical data that should be provided:

- the weight of the IOL;
- material homogeneity viewed at 10X magnification;
- surface quality viewed at 10X magnification; and
- edge quality viewed at 10X magnification.

Product Information / Instructions for Use / Promotional Material

Where specific cleaning and/or disinfection solutions or accessories are required for the device, a description of containers, composition of solutions, any equipment needed, and their specifications, are required.

Testing — Mechanical Data

Information is required on the mechanical properties of all IOLs that:

- incorporate an IOL design radically different to that of a currently registered IOL; or
- are intended to be fixed in a position that may place additional stress on the intraocular tissue; or
- are intended to be fixed in a position other than the posterior chamber; or
- are made from a material different to that of a currently registered IOL; or
- are manufactured by a process significantly different to that of a currently registered IOL; or
- fall within one of the minor modification parameters above, e.g. a minor formulation change in optic or haptic material, that may require evidence to show that the mechanical properties of the modified lens are not significantly different from the predicate model; or
- incorporate any change in any manufacturing process, technological characteristics or intended use that may adversely affect the mechanical properties of the IOL.

The manufacturer must determine which of the tests below are applicable and provide a rationale for their selection as not all of the following tests will be applicable for every application:

- compression force testing;
- compression force as a function of contact angle per haptic;
- compression force after decay as a function of contact angle per haptic;
- optic decentration testing;
- optic tilt testing;
- axial displacement during compression testing;
- fatigue testing;
- haptic pull strength testing.

Details on all testing procedures should include scope, method (including diagrams if applicable), results, discussion and conclusion(s) of testing.

Manufacturing / Quality Control / Sterility

Manufacturing Process

Full details of the manufacturing process, including assembly, postfabrication, testing, packaging and sterilization are required for all IOLs where the manufacturing method cannot be equated to that of a currently registered IOL from the same manufacturer. The sponsor may also refer to a previously submitted GMP plant master file. The following are required:

- details of site interfaces (transfer of products from one site to a different site);
- details of any manufacturing processes provided by third party (contract) manufacturers; and
- details of any manufacturing process which is critical to the device.

Biocompatibility / Preclinical

Biological Safety and Biocompatibility Testing

Details must be provided on:

- biological safety studies performed on the finished device and on representative component samples from the final product or materials; and
- biocompatibility studies, i.e. device-specific functional studies; and
- any other in vitro or in vivo studies carried out on the finished device, especially those relating to long term leachability, stability and durability.

Evaluation of the biocompatibility and biological safety characteristics is required for all IOLs where the biocompatibility and biological safety characteristics cannot be equated to a currently registered IOL. If equivalence cannot be claimed, biocompatibility and biological safety data must be provided as per Chapter 2.7 *Biological Safety and Biocompatibility Testing.*

Internationally acceptable standards for IOLs include:

- ANSI Z80.7 *Ophthalmics Intraocular Lenses* (current edition is 1994);
- the FDA document — *Intraocular Lens (IOL) Guidance Document* (an Oct 1997 draft is the most recent);
- the ISO standard 11979-5 *Optics and Optical Instruments — Intraocular lenses Part 5:Biocompatibility* (currently an ISO/DIS dated Dec 1997).

The pass/fail criteria for intraocular lens testing must comply with the requirements in these standards.

If appropriate, testing specific to IOLs should also include:

- photostability against UV irradiation;
- stability against Yttrium Aluminium Garnet (YAG) laser exposure.

Preclinical

The following information is required:

- the effects of the implant of the device on fluids and tissues,
- results of all functional in vivotesting of the device in experimental animal models.

Human Clinical Data

Generally, presentation of Clinical Data should be based on Chapter 2.8*Human Clinical Data.* The draft International standard ISO 11979.7 *Optics and Optical Instruments*: *Intraocular Lenses Clinical Investigations* may be a useful guide for submitting Clinical data. However, there are specific requirements in this area for IOLs.

IOLs Requiring Clinical Data for 500 Patients

Clinical studies involving at least 500 patients' clinical data, with a minimum follow-up of 12 months, are required if the IOL is:

- from a manufacturer which currently has no other IOLs registered in Australia; or
- a new, radically different IOL design that cannot be equated to an IOL that is currently registered; or
- a new non-posterior chamber (PC) IOL, or a modification, which is not considered to be minor, to a non-PC IOL (minor modifications are defined below in *IOLs requiring no clinical data* (*Minor modifications to currently registered IOLs*) and *Minor modification parameters*); or
- a new multifocal IOL, or a modification, that is not considered to be minor, to a multifocal IOL; or
- made from a material other than PMMA; where
  - the material cannot be equated to a currently registered IOL, or
  - the material is sourced from a manufacturer who has never sourced that particular material for the purpose of manufacturing predicate IOLs,
  - the raw material processing steps cannot be equated to those of a currently registered IOL; or
- manufactured by a process significantly different from any other process used to manufacture IOLs, for that particular manufacturer.

IOLs Requiring Clinical Data for 100 Patients

Clinical studies involving at least 100 patients' clinical data, with a minimum follow-up of 6 months, are required if the IOL is:

- a modification to a currently registered non-PC IOL, which is considered to be minor and does not affect the safety, quality or efficacy of the IOL; or
- a modification to a currently registered multifocal IOL, which is considered to be minor and does not affect the safety, quality or efficacy of the IOL; or
- does not fit into a category of IOLs requiring 500-patient data described above, or into a category not requiring clinical data given below.

For modifications to the design of a currently registered IOL, which have a significant effect on the optical, mechanical or physical properties of the IOL, it is the responsibility of the sponsor to justify whether the modification requires 500 or 100 patients' clinical data. The sponsor should support the justification with detailed optical, mechanical and physical data.

IOLs Not Requiring Clinical Data

No clinical studies are required if the IOL is considered to be a minor modification of a currently registered IOL. An IOL may be considered to be a minor modification to a currently registered IOL, if:

- it is monofocal and intended to be implanted in the posterior chamber (PC); and
- it is manufactured from the same material (and surface modification if applicable); and
- the lens raw material is manufactured by the same method and manufacturer; and
- the overall lens manufacture remains unchanged; and
- the currently registered IOL has been subjected to a full evaluation, including clinical data; and
- the changes in lens parameters fall within the design characteristics specified in the *Minor Modification Parameters* below.

Minor Modification Parameters

The following is a list of the IOL parameters for which the stated modifications are considered to be minor:

- right- or left-handed version of a model;
- change in overall lens diameter within the range of 10.5 mm (capsular placement) or 11.0 (ciliary sulcus placement) to 14.5 mm;
- the addition of notches, loops or rounded ends to haptics;
- change in haptic angulation, in the range 0 to 10 degrees (optic angulated posterior to the haptics);
- change in haptic design, configuration or calibre which has no significant effect on the mechanical properties of the lens (refer to *Mechanical Data* above);
- change in the dioptric power range. For soft materials such as silicone and hydrogels, the sponsor should provide evidence to show that the change in dioptric power does not adversely affect the optical qualities of the lens.
- change in the optic diameter within the range 7.5 mm to 5.5 mm (ciliary sulcus placement) or 5.0 mm (capsular placement);
- addition, deletion or moving of positioning holes on the optic— unless they infringe on the central 4.25 mm of the optic;
- addition of a ridge on the posterior surface of the optic (unless the ridge infringes on the central 4.25 mm of the optic), or modification of the optic for weight reduction purposes;

- change in the optic shape factor (e.g. planoconvex, biconvex, etc.) or a change in the optic from a circular to another shape (e.g. elliptical) where this is not the first such change, or where the change is not intended to produce more than one focal point;
- a minor formulation change in optic or haptic material (e.g. the addition of a dye to a haptic, a change in crosslinking agent, the addition or deletion of a UV absorber, the use of a copolymeric material with a slightly different ratio of the two principal monomers) which results in no measurable alteration in the mechanical surface (refer to *Mechanical Data* above), or leaching characteristics (e.g. rate, identity) of the material;
- change in optic material in a 3-piece model. A sponsor may substitute the optic material in a lens design for an optic material from a previously approved lens, provided that the lens design and optic material are from the same manufacturer. In all cases, both the approved design and the substituted optic material must have been evaluated and approved by the Department. The sponsor must demonstrate that the change in optic material does not alter the mechanical properties of the approved design and must also demonstrate that the optical properties (refer to *Mechanical Data* above) of the approved design are not compromised. The manufacturers must be able to demonstrate that they possess the proven technology to manufacture the modified lens.
- change in haptic material to a material used in a previously approved lens. In all cases, both the approved design and the substituted haptic material must have been evaluated and approved by the Department. The sponsor must demonstrate that the change in haptic material does not alter the mechanical properties of the approved design (refer to *Mechanical Data* above).

The manufacturer must be able to demonstrate the competence to apply the technology required to manufacture the modified lens. Such a change must be notified on the form 'Therapeutic Devices Application' and must be accompanied by a statement giving the registration and product numbers of the registered lens, the design characteristics which have been altered, and the change in parameters.

Depending on the modification, an application for a minor modification to a lens may require additional data to show that the mechanical, optical and physical properties of the lens have not been compromised by the modification.

Minor modifications now include IOLs made from materials other than PMMA, e.g. silicone and hydrogels. Minor modifications to PMMA lenses may fall into the listable category and as such may not require evaluation. Before submitting an application for a PMMA minor modification, the sponsor should first check if the IOL is listable.

For all minor modification applications, the sponsor must show how the modified IOL is related to a lens on which clinical studies have been collected, or a lens which has been *grandfathered.*

Ch. 2.16 Intraocular Lenses (IOL)

Please include this completed checklist with your submission

A tick ✓ indicates information that is to be supplied as part of the submission

Fee Structure	Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.16	Reference Vol/Page
	General Details	✓		/
	Risk Analysis	✓		/
	Table of Equivalence #	✓	✓	/
	Commercial and Regulatory History	✓		/
	GMP	✓		/
	Reporting Conditions	✓		/
	Postmarket Surveillance	✓		/
	Samples	✓	✓	/
	Quarantine ##	✓		/
Design/	Design and Construction	✓	✓	/
Materials/	Materials	✓		/
	Labelling	✓		/
	Packaging	✓		/
	PI/Instructions for Use/PM **	✓	✓	/
				/
Testing	Testing	✓	✓	
Manufacturing/	Manufacturing	✓	✓	/
Quality Control/	Quality Control	✓		/
Sterility	Sterility	✓		/
Biocompatibility/	Biological Safety/Biocompatibility Testing	✓	✓	/
Preclinical (in vivo)	Preclinical (in vivo)	✓	✓	/
Human Clinical Data	Human Clinical Data	✓	✓	/

\# to be provided if equivalence to a predicate device is being claimed

should comply with AQIS requirements for imported devices containing human and animal derived material

** Product Information/Instructions for Use/Promotional Material

Ch. 2.16 Intraocular Lenses (IOL) — Table of Equivalence

If Equivalence is being sought for a reduction in evaluation fees
*please include this **completed** Table of Equivalence with your submission*

Please indicate ✓ where *Predicate* and *Equivalent* Information is supplied, and reference details within the submission

Fee Structure	Evaluation Categories	✓ Registered Predicate Device	✓ Equivalent information New Device	Reference Vol/Page
Design/	Design and Construction	_____	_____	/
Materials/	Materials	_____	_____	/
	Labelling	_____	_____	/
	Packaging	_____	_____	/
	PI/Instructions for Use/PM **	_____	_____	/
Testing	N/A			
Manufacturing/	Manufacturing	_____	_____	/
Quality Control/	Quality Control	_____	_____	/
Sterility	Sterility	_____	_____	/
Biocompatibility/	Biological Safety/Biocompatibility Testing	_____	_____	/
Preclinical (in vivo)	Preclinical (in vivo)	_____	_____	/
Human Clinical Data	Human Clinical Data			/

** Product Information/Instructions for Use/Promotional Material

2.17 INTRAOCULAR VISCOELASTIC FLUIDS (IOF)

Viscoelastic fluids are classified as registrable devices if they are used in ophthalmic surgery. They may be indicated to:

- aid in filling space upon loss of ocular fluid or tissue; and
- reduce endothelial cell damage and trauma from instruments or an intraocular lens by acting as a protective layer.

Viscoelastic fluids, synthetically produced or derived from animal or human material, and used in the defined indication, must be approved for registration in the ARTG before importation and supply may occur in Australia.

Additional requirements are specified in Chapter 2.10 *Animal Origin Devices* or Chapter 2.15 *Human Origin Devices* for human- or animal-derived intraocular viscoelastic fluid whichever is relevant.

Sponsors for registration of synthetic viscoelastic fluids are not required to complete the questionnaire section titled *Source Materials and Risk of Infectivity*, in either chapter.

Each registrable device submission must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

General Details

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Risk Analysis

Refer to Chapter 2.5 *Risk Analysis*.

Table of Equivalence

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*.

Commercial and Regulatory History

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice

Refer to Chapter 1.19 *Good Manufacturing Practice.*

Reporting Conditions
Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance
Refer to Chapter 1.6 *Postmarket Compliance Programs.*

Samples
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Biocompatibility / Preclinical

Biological Safety / Biocompatibility Testing
Performance Characteristics of Viscoelastic Fluids for Intraocular Indications
In addition to the requirements outlined above, sponsors should provide details of test protocols, results, conclusions and summaries of the following tests and studies:

- chemical properties
  - solubility,
  - purity,
  - pH,
  - freedom from particles;
- physical properties to be measured at storage temperature and at 30^0C
  - zero shear viscosity,
  - viscoelasticity,
  - pseudoplasticity,
  - cohesiveness and coatability.

Human Clinical Data

Submissions for the viscoelastic fluids

- sodium hyaluronate extracted from rooster combs;
- chondroitin sulphate from shark cartilage; or
- compounds of both;

which are manufactured using known technology and intended for use in intraocular surgery are not required to include Human Clinical Data for evaluation.

All other submissions for intraocular viscoelastic fluids for intraocular surgery must include Human Clinical Data.

Ch. 2.17 Intraocular Viscoelastic Fluids

Please include this completed checklist with your submission

A tick ✓ indicates information that is to be supplied as part of the submission

Fee Structure	Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.17	Reference Vol/Page
	General Details	✓		/
	Risk Analysis	✓		/
	Table of Equivalence #	✓		/
	Commercial and Regulatory History	✓		/
	GMP	✓		/
	Reporting Conditions	✓		/
	Postmarket Surveillance	✓		/
	Samples	✓		/
	Quarantine ##	✓		/
Design/	Design and Construction	✓		/
Materials/	Materials	✓		/
	Labelling	✓		/
	Packaging	✓		/
	PI/Instructions for Use/PM **	✓		/
Testing	Testing	✓		/
Manufacturing/	Manufacturing	✓		/
Quality Control/	Quality Control	✓		/
Sterility	Sterility	✓		/
Biocompatibility/	Biological Safety/Biocompatibility Testing	✓	✓	/
Preclinical (in vivo)	Preclinical (in vivo)	✓		/
Human Clinical Data	Human Clinical Data	✓	✓	/

\# to be provided if equivalence to a predicate device is being claimed

should comply with AQIS requirements for imported devicescontaining human and animal derived material

** Product Information/Instructions for Use/Promotional Material

Ch. 2.17 Intraocular Viscoelastic Fluids — Table of Equivalence

If Equivalence is being sought for a reduction in evaluation fees
*please include this **completed** Table of Equivalence with your submission*

Please indicate ✓ where *Predicate* and *Equivalent* Information is supplied, and reference details within the submission

Fee Structure	Evaluation Categories	✓ Registered Predicate Device	✓ Equivalent information New Device	Reference Vol/Page
Design/	Design and Construction	_____	_____	/
Materials/	Materials	_____	_____	/
	Labelling	_____	_____	/
	Packaging	_____	_____	/
	PI/Instructions for Use/PM **	_____	_____	/
Testing	N/A			
Manufacturing/ Quality Control/ Sterility	Manufacturing	_____	_____	/
	Quality Control	_____	_____	/
	Sterility	_____	_____	/
Biocompatibility/ Preclinical (in vivo)	Biological Safety/Biocompatibility Testing	_____	_____	/
	Preclinical (in vivo)	_____	_____	/
Human Clinical Data	Human Clinical Data			/

** Product Information/Instructions for Use/Promotional Material

2.18 INTRAUTERINE CONTRACEPTIVE DEVICES (IUCD)

Intrauterine contraceptive devices (IUCDs) are classified as registrable devices, unless the principal contraceptive action of the IUCD is achieved chemically through the release of a drug. In that case the IUCD will be treated as a drug, and the requirements set out in the TGA publication *Australian Guidelines for the Registration of Drugs*, Volume 1: *Prescription and Other Specified Drug Products* available from the TGA Publications Office, will apply.

Each registrable device submission must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

The device information should be formatted according to DR4 and should be submitted in volumes separate from the drug information.

General Details
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Risk Analysis
Refer to Chapter 2.5 *Risk Analysis*.

Table of Equivalence
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Commercial and Regulatory History
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice
Refer to Chapter 1.19 *Good Manufacturing Practice.*

Reporting Conditions
Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance
Refer to Chapter 1.6 *Postmarket Compliance Programs.*

Samples
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Design / Materials / Testing

Design / Construction

Detailed descriptions of the device, its clinical purpose, how the device functions and any special features (e.g. whether it acts as a foreign body, metal releasing, drug releasing, with added side effect controlling features, etc.) are required.

Engineering drawings of the assembled IUCD, components and accessories are required. The submission must justify the design rationale in relation to IUCD insertion, intrauterine contraceptive activity, intrauterine device stability and removal. Specifications for tensile strength of any attached filamentous tail and the method and strength of its attachment to the device must be included. The tail should be a monofilament and non-biodegradable.

The IUCD should be radio-opaque and designed so that it is easily removable.

Labelling

Copies of the labels fixed to the device unit and outer packaging for supply in Australia shall conform to TGO 37 *General Requirements for Labels for Therapeutic Devices* (see Appendix 16), and must include the:

- product name and description;
- sponsor/manufacturer's name and address;
- country of manufacture;
- batch number (lot, serial number, etc.);
- storage conditions;
- date of manufacture **and** shelf life, or expiry date on the packaging;
- the word 'sterile' if the device is supplied sterile.

Product Information / Instructions for Use / Promotional Material

In addition to the general requirements for product literature in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*, the following information should be supplied with the device and therefore will be evaluated as part of the submission:

- copies of prescribing information and instructions for use; they should address:
  - contraindications for use;
  - the recommended time and technique for insertion;
  - the use of any accessory inserting device;
  - any trimming of withdrawal tail;
  - any complications during insertion;
  - the recommended maximum in utero residence time;
  - the techniques for location in situ;
  - the techniques for removal; and
  - the details of shelf life and storage conditions;

- a copy of consumer information, written in Plain English, fully describing the use, effectiveness and other educational features, contraindications, warnings; e.g.
  - name and a descriptive diagram of the IUCD;
  - recommended removal time;
  - details of any possible side effects and complications (and recommended action); and
  - instructions for checking for the position;
- copies of any promotional or advertising material concerning the device, components and accessories.

Testing

Details of all laboratory and bench testing of either the assembled device or its component parts and the rationale for the acceptance criteria on the test are required. Evidence must be provided that the physical strength/stability and contraceptive potential are satisfactorily maintained throughout the recommended life span of the device.

Tests should include, but are not limited to, the:

- tensile properties of the body and tail of the IUCD;
- fatigue studies, stress cracking;
- determination of leachable substances and material degradation;
- SEM examination of the device surface for irregularities;
- kinetics of metal/drug release;
- effect of aging in a simulated uterine environment on the tensile properties and stability of the device.

Manufacturing / Quality Control / Sterility

Manufacturing Process

Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices* gives an overview of the information required for evaluation of the manufacturing process. A complete description of the steps used in manufacture and testing of the IUCD is required, e.g.

- polymer extrusion, moulding;
- incorporation of radio-opaque substance;
- incorporation of contraceptive drug/metal ion releasing component, including its distribution in the IUCD and the method of tail attachment to the body of the device.

Ch. 2.18 Intrauterine Contraceptive Devices (IUCD)

Please include this completed checklist with your submission

A tick ✓ indicates information that is to be supplied as part of the submission

Fee Structure	Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.18	Reference Vol/Page
	General Details	✓		/
	Risk Analysis	✓		/
	Table of Equivalence #	✓		/
	Commercial and Regulatory History	✓		/
	GMP	✓		/
	Reporting Conditions	✓		/
	Postmarket Surveillance	✓		/
	Samples	✓		/
	Quarantine ##	✓		/
Design/	Design and Construction	✓	✓	/
Materials/	Materials	✓		/
	Labelling	✓	✓	/
	Packaging	✓		/
	PI/Instructions for Use/PM **	✓	✓	/
				/
Testing	Testing	✓	✓	
Manufacturing/	Manufacturing	✓	✓	/
Quality Control/	Quality Control	✓		/
Sterility	Sterility	✓		/
Biocompatibility/	Biological Safety/Biocompatibility Testing	✓		/
Preclinical (in vivo)	Preclinical (in vivo)	✓		/
Human Clinical Data	Human Clinical Data	✓		/

\# to be provided if equivalence to a predicate device is being claimed

should comply with AQIS requirements for imported devices containing human and animal derived material

** Product Information/Instructions for Use/Promotional Material

Ch. 2.18 Intrauterine Contraceptive Devices — Table of Equivalence

If Equivalence is being sought for a reduction in evaluation fees
*please include this **completed** Table of Equivalence with your submission*

Please indicate ✓ where *Predicate* and *Equivalent* Information is supplied, and reference details within the submission

Fee Structure	Evaluation Categories	✓ Registered Predicate Device	✓ Equivalent Information New Device	Reference Vol/Page
Design/	Design and Construction	_____	_____	/
Materials/	Materials	_____	_____	/
	Labelling	_____	_____	/
	Packaging	_____	_____	/
	PI/Instructions for Use/PM **	_____	_____	/
Testing	N/A			
Manufacturing/	Manufacturing	_____	_____	/
Quality Control/	Quality Control	_____	_____	/
Sterility	Sterility	_____	_____	/
Biocompatibility/	Biological Safety/Biocompatibility Testing	_____	_____	/
Preclinical (in vivo)	Preclinical (in vivo)	_____	_____	/
				/
Human Clinical Data	Human Clinical Data			/

** Product Information/Instructions for Use/Promotional Material

LOW LEVEL REGISTRABLE DEVICES

Specfic low level Registrable device policies	chap
Barrier contraceptive devices	2.19
	2.20
Breast prostheses (saline)	
Disinfectants:	2.21
Instrument grade Sterilants	
Hospital grade with claims	
HIV/HCV in vitro diagnostics	2.22

Registrable devices included in Schedule 3 Part 2 (Therapeutic Devices Attracting a Lower Fee) of the *Regulations* are described below.

Devices for which a Standard has been Determined

This category is limited to:

- therapeutic devices, to which a standard determined under subsection 10(1) of the Act applies, that are bedside or ambulatory infusion pumps.

In addition to satisfactory evidence of GMP, the sponsor must:

- submit a Test Certificate of a batch representative of those to be supplied in Australia (but not necessarily one which will be supplied in Australia), consisting of a detailed certificate of compliance with the specified Order from an approved laboratory, with comments against each requirement of the Order; and
- be able to demonstrate compliance with the Order for all subsequent batches supplied in Australia, when requested by the TGA. Where a certificate has not been obtained prior to supply of the batch, this certificate may be produced within a reasonable time, from a retention sample if necessary.

Other Devices

Other devices in the low fee-level registration category are:

- implantable breast prostheses containing material of fluid consistency, except:
  - those listed in Schedule 3, Part 1; and
  - tissue expanders which are filled using only water or saline solution and which are not intended by the manufacturer to be left permanently in place;
- devices that are barriers indicated for contraception or for prevention of the transmission of disease in the course of penile penetration during sexual intercourse, other than rubber diaphragms and condoms that conform to a standard under Subsection 10(1) of the Act;
- sterilants and instrument grade disinfectants, hospital grade disinfectants with specific claims, household and commercial grade disinfectants with specific claims;
- in vitro diagnostic goods used for the diagnosis of patients infected with Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV).

2.19 BARRIER CONTRACEPTIVE DEVICES

Barrier contraceptives to which a Standard does not apply (e.g. female condom, cervical cap), are **Low Level Registrable Devices** (*Therapeutic Goods Regulations*, Schedule 3 Part 2). Information, tests and data submitted will be assessed for their applicability to the device's intended use. Depending on the nature of the device it may be necessary to raise further issues for evaluation during the course of the evaluation itself.

Each registrable device submission must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

General Details
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Risk Analysis
Refer to Chapter 2.5 *Risk Analysis*.

Commercial and Regulatory History
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice
Refer to Chapter 1.19 *Good Manufacturing Practice.*

Reporting Conditions
Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance **Error! Bookmark not defined.**
Refer to Chapter 1.6 *Postmarket Compliance Programs.*

Samples
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Design / Construction
The following design characteristics must be fully described:

- the shape and dimensions;
- any special design features;
- the inserter design, including physical characteristics;
- insertion procedures, if applicable (if device does not have an inserter, the insertion procedure must be described; and
- the removal procedures.

Labelling

Additional information to be exhibited on the label includes the:

- date of manufacture;
- shelf life, or expiry date;
- storage conditions.

Product Information / Instructions for Use / Promotional Material

All literature provided with, or used in the marketing of, the device must be included in the submission. This includes, but is not limited to:

- copies of any information provided separately to professional or family planning staff, including any training or instructional literature, video cassettes, visual aid materials;
- copies of product inserts and user information. Consumer information must be written in Plain English, fully describing the use, effectiveness and other educational features, contraindications, warnings and methods of disposal;
- copies of any promotional or advertising material concerning the device, components and accessories.

Testing — Chemical and Mechanical Properties

Sponsors should provide the protocols and results (including the raw data) of tests performed on samples taken from at least three production batches in order to validate the materials and design of the final product. Details are also required about:

- the material types and their suppliers, if standards are applicable; or
- the material suppliers, the percentage composition of the materials, together with details of the mixing, forming and curing processes; and
- the components in the completed device and procedures for their quality control, including identity and quantification of extractable residues;
- the uniformity and texture of the device surface, as determined by surface scanning electron microscopy (SEM) or other appropriate methods;
- the tensile strength, tear strength, freedom-from-holes test, elasticity and other measures of the flexural characteristics of the device and its component materials, as well as the vulnerability to puncture.

The expected batch size (i.e. devices produced during a single manufacturing cycle) also needs to be determined.

Biological Safety / Biocompatibility Testing

Stability

Details must be provided of studies of the physical and chemical properties of the finished device following prolonged exposure (real time and accelerated aging) to lubricants/spermicides (if applicable), transit, storage and the biological environment in which it is to be used. Test results must support the shelf life claimed for the device.

Toxicity

The toxicity of component materials of the finished device should be evaluated by appropriate in vitro and in vivo toxicological studies, e.g. cytotoxicity, sensitisation and irritation tests, and examination of device influence on the microbial flora of the intended environment. *ISO 10993-1:1997 Biological Evaluation of Medical Devices — Part 1: Evaluation and Testing* may be useful for selecting the appropriate types of tests.

Barrier Properties to Sexually Transmitted Pathogens

This section only applies if the sponsor claims that the device will assist in the prevention of a Sexually Transmissible Disease (STD)

It is essential that the device under study be an effective physical barrier to bacterial and viral STD agents. Barrier performance of the device can be demonstrated by using test particles (e.g. microspheres, radio labelled tracers, viruses, etc.) less than or equal to 42 nm in diameter, the size of the smallest known STD microorganism (i.e. Hepatitis B virus).

- Test conditions should simulate actual use. The new barrier device must be compared with an established (reference) device, such as the latex (rubber) condom. The barrier performance of the new device must be shown to be equal to, or to exceed, that of the reference device.
- The test conditions that differ from actual use conditions, and which may affect the comparison of barrier performance, must be justified. Conditions which may be important include temperature, pH, viscosity, the surface tension of the fluid and the wetting angle of the barrier, physical and chemical properties of the test solutes, and other testing conditions such as the magnitude of applied pressure (steady or transient), barrier membrane stress or deformation, etc.
- The test methodology must be sufficiently sensitive to evaluate the permeability of the reference device, particularly with respect to the size of the particle, as stated above, and sufficient numbers of devices of each type should be tested to provide a statistically significant comparison.

Human Clinical Data

A summary of data, generated in documented clinical trials, must be provided to support each specific claim for clinical effectiveness.

Studies should be designed to determine the feasibility, acceptability, fit, size, etc. and the safety of the device. These studies should evaluate the following:

- any potential adverse effects, including:
  - mucosal irritation and sensitisation;
  - microbial flora of the vagina, cervix and device;
  - vaginal and cervical cytology;
  - trauma;
  - ulceration;
  - urinary tract infection;
  - bleeding;
  - salpingitis;
  - pain; and discomfort;
- device wear-time and device displacement and/or expulsion (the device must remain in place for the intended duration); and
- post-coital testing. Documentation should include Papanicolaou (Pap) smears. Pap smears should be evaluated at a single clinical laboratory in order to maintain consistency in observation criteria.

Selection and Exclusion Criteria

The study subjects must be protected by using an effective, non-barrier means of contraception (oral contraceptives, IUD or tubal sterilization).

Investigator Selection Criteria

An investigator must be knowledgeable about all types of contraception and experienced in managing patients who use barrier contraceptive methods. The investigator must be willing to closely monitor each study subject and maintain a reasonable follow-up procedure.

Study Size and Duration

The study should include at least 50 female study subjects, with at least 10 coital episodes per subject, giving a total of at least 500 assessable coital episodes.

Ch. 2.19 Barrier Contraceptive Devices

Please include this completed checklist with your submission

A tick ✓ indicates information that is to be supplied as part of the submission

Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.19	Reference Vol/Page
General Details	✓		/
Risk Analysis	✓		/
Commercial and Regulatory History	✓		/
GMP	✓		/
Reporting Conditions	✓		/
Postmarket Surveillance	✓		/
Samples	✓		/
Quarantine ##	✓		/
Design and Construction		✓	/
Materials			/
Labelling		✓	/
Packaging			/
PI/Instructions for Use/PM **	✓	✓	/
Testing		✓	/
Manufacturing			/
Quality Control			/
Sterility			/
Biological Safety/Biocompatibility Testing	✓*	✓	/
Preclinical (in vivo)		✓	/
Human Clinical Data		✓	/

should comply with AQIS requirements for imported devices containing human and animal derived material

** Product Information/Instructions for Use/Promotional Material

* Some testing according to principles in Chapter 2.7 *Biological Safety and Biocompatability Testing*

2.20 BREAST PROSTHESES (SALINE)

Breast prostheses containing **only saline** which are manufactured using established materials and technology and are intended by the manufacturer to be left permanently in place are classified as low level registrable devices. Evaluation of the physical, chemical and biological properties, including all finished product specifications, is required.

Each registrable device submission must comply with the *General Details* section in Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices*. Provision of any additional information will be stipulated below. The checklist at the end of this chapter provides a summary of the general and additional information required by the TGA, and sponsors are required to include a completed checklist with their submission.

General Details
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Risk Analysis
Refer to Chapter 2.5 *Risk Analysis*.

Table of Equivalence
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Commercial and Regulatory History
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice
Refer to Chapter 1.19 *Good Manufacturing Practice.*

Reporting Conditions
Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance
The submission must address the following points:

- the issue of device marking to enable identification of the make, model and batch number of the implant by some imaging modality;
- the details of procedures for maintaining a database of patient and device identification;
- the details of the system for obtaining and processing problems with the device.

Refer also to Chapter 1.6 *Postmarket Compliance Programs.*

Samples
Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Design / Construction
The submission must describe the design specifications of the breast prosthesis, e.g. shape, volume/s, seams/seals, surface characteristics, valve.

Testing — Integrity of the Shell Material
Details of all test protocols, results and conclusions of the following tests and studies must be submitted:

- pore size/diffusion potential;
- impact resistance;
- rupture rates;
- resistance to abrasion;
- elastic modulus and tensile properties;
- fatigue testing and ageing.

If resterilization is an option, details must be provided of the effect of the process on the stability of the device.

Testing — Integrity of the Valve
The reliability of the valve, if fitted, and any associated inflation mechanism, has to be demonstrated, along with the details of the test protocol, results and conclusion(s).

Biological Safety and Biocompatibility Testing
Information on the biological safety and biocompatibility testing of the device should be submitted if:

- the raw materials have not been previously evaluated and marketed for this proposed indication in Australia, or
- a change has occurred in the material processing during manufacture.

If materials have been previously marketed in Australia for implants, the submission must list all the products in which these materials are used.

The following information relating to the shell material is required:

- a description of the in vivo biokinetics of the material including the kinetics and pharmacological activity of all extractable and biodegradation products under the following headings:
  - metabolism;
  - absorption;
  - excretion;
  - distribution;
  - other, e.g. protein binding, enzyme induction or inhibitions; and
  - changes in physical and material properties;
- a description of mode of administration of material, species and number of animals used and parameters studied.

Details of the immunological potential of the materials must be provided. Humoral and cell mediated responses should also be investigated. Refer to Chapter 2.7 *Biological Safety and Biocompatibility Testing* for more information.

Human Clinical Data

Provide a description of the clinical indications for the prosthesis, and give a summary of data which establish its clinical safety. Refer to Chapter 2.8 *Human Clinical Data.*

Ch. 2.20 Breast Prostheses (Saline)

Please include this completed checklist with your submission

A tick ✓ indicates information that is to be supplied as part of the submission

Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.20	Reference Vol/Page
General Details	✓		/
Risk Analysis	✓		/
Commercial and Regulatory History	✓		/
GMP	✓		/
Reporting Conditions	✓		/
Postmarket Surveillance	✓		/
Samples	✓		/
Quarantine ##	✓		/
Design and Construction		✓	/
Materials	✓		/
Labelling	✓		/
Packaging	✓		/
PI/Instructions for Use/PM **	✓		/
Testing		✓	/
Manufacturing			/
Quality Control			/
Sterility			/
Biological Safety/Biocompatibility Testing	✓	✓	/
Preclinical (in vivo)			/
Human Clinical Data	✓	✓	/

should comply with AQIS requirements for imported devices containing human and animal derived material

** Product Information/Instructions for Use/Promotional Material

2.21 DISINFECTANTS AND STERILANTS

Information to be supplied with an application for registration or listing of disinfectants and sterilants in the ARTG is described in Appendix 18,*TGO 54, 54A and Guidelines — Standard for Composition, Packaging, Labelling and Performance of Disinfectants and Sterilants.*

Other documents contained in Appendix 18 include the*ARTG Standardised Data Requirements For Disinfectants and Sterilants*, and the draft documents, *Changes to Disinfectants and Sterilants Included in the ARTG as Therapeutic Devices — Is Notification or Prior Approval Required?* and *Advertising Guidelines for Disinfectants and Sterilants.* (The draft documents when approved will be updated in the Appendix). This Appendix may also serve as a guide to the sponsors of other products that have to meet TGO 54, but which are exempt from the requirement for registration or listing.

Table 2.2. Classification, Labelling and GMP Licensing Requirements for Disinfectants and Sterilants

<table>
<tr><th>Product Classification</th><th>Australian Register of Therapeutic Goods (ARTG)</th><th>Labelling Requirements</th><th>GMP Licensing</th></tr>
<tr><td>Sterilant</td><td rowspan="6">Registrable

(Schedule 3 Part 2)</td><td rowspan="6">TGO 54

& TGO 54A</td><td rowspan="4">Manufacturer

Licensing

Required</td></tr>
<tr><td>High Level — Instrument Grade</td></tr>
<tr><td>Intermediate Level — instrument Grade</td></tr>
<tr><td>Low Level — Instrument Grade</td></tr>
<tr><td>Hospital Grade with specific claims</td><td rowspan="2">Not

Required</td></tr>
<tr><td>Household /Commercial Grade with specific claims</td><td>+ AUST R</td></tr>
<tr><td>Hospital Grade without specific claims</td><td>Listable</td><td>TGO 54

& TGO 54A

+ [AUST L]*</td><td>Not

Required</td></tr>
<tr><td>Household /Commercial Grade without specific claims</td><td rowspan="4">Exempt</td><td rowspan="4">TGO 54

& TGO 54A</td><td rowspan="4">Not

Required</td></tr>
<tr><td>Sanitisers**</td></tr>
<tr><td>Sanitary fluid**</td></tr>
<tr><td>Antibacterial clothes preparation</td></tr>
</table>

Note * [AUST L] indicates that an AUST L number on the label is not mandatory but its use is encouraged

** Sanitisers / Sanitary fluids except for those specified in *Excluded Goods Order No.1 of 1997* (see Appendix 7).

Sponsors should also refer to the following:

Sponsors should also refer to the following:
Chapter 1.19 *Good Manufacturing Practice*,
GMP — Standard of Overseas Manufacturers (see Appendix 10),
Excluded Goods (see Appendix 7), and
Exempt Goods (see Appendix 8).

Application procedures are contained in the guidelines document attached to TGO 54. Applications for registration will be subject to evaluation by the Conformity Assessment Branch (CAB) and the Therapeutic Goods Administration Laboratories (TGAL) Branch, in accordance with Section 25 of the *Therapeutic Goods Act 1989*. Applications for listing will be reviewed by CAB in accordance with Section 26 of the Act.

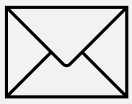
2.22 HIV/HCV IN VITRO DIAGNOSTIC KITS

Following amendments to the *Therapeutic Goods Regulations* effective 1 October 1995, in vitro diagnostics for the diagnosis of patients infected with the Human Immunodeficiency Virus (HIV) or with the Hepatitis C virus (HCV) are required to be registered in the ARTG.

If the application is acceptable, the CAB will advise the sponsor of the evaluation fee, any additional data required and the number of test kits required for evaluation. All data for evaluation must be sent to the CAB who will coordinate the evaluation. The TGA undertakes the evaluation of kit integrity while the quality and efficacy aspects are evaluated by the National Serological Reference Laboratory (NRL) located in Melbourne.

Separate applications for registration must be made for each distinct product, although different pack sizes can be included under a single registration. Antigen and antibody control panels are considered to be kit accessories and are included in the test kit registrations. All kit components and accessories must be specified in the application. Refer to Chapter 1.9 *Reducing Annual Charges* and Chapter 3.25 *Kits.*

Further information may be obtained from:



Conformity Assessment Branch, TGA
MDP 122
PO Box 100,
WODEN, ACT 2606

ph: 02 6232 8674
fax: 02 6232 86

Conditions of Registration

HIV Test Kits

Test kits will be entered in the ARTG and specified as being suitable for routine screening or supplemental purposes. The conditions relating to the registration will specify the appropriate category.

Sponsors will be advised by the TGA of the marketing approval, which will include details of the ARTG registration number, conditions of approval and the certificate of registration.

HCV Test Kits

Test kits are categorised as being suitable either for routine screening or for supplemental purposes only, and the condition of entry in the ARTG will specify the category of supply.

There is no restriction to the supply of HCV test kits approved for screening once entered in the ARTG. However, it is Commonwealth policy that all HCV test kits approved for use as supplemental assays and those using newer technology (such as polymerase chain reaction, branched DNA amplification or procedures currently in developmental stages) be supplied only to laboratories approved by State/Territory health authorities.

Use of Unapproved HIV/HCV Test Kits

Provisions exist for the supply of unapproved HIV/HCV test kits either for research use or under the Clinical Trials / Special Access Schemes in the *Therapeutic Goods Act 1989*. Refer to Chapter 1.24 *Access to Unapproved Therapeutic Devices.*

The following criteria apply to the supply of unapproved IVDs either for use in a Clinical Trial or for Research Use. The sponsor must ensure that:

- approval is obtained from the Institutional Ethics Committee according to the NHMRC guidelines;
- a protocol with appropriate objectives has been developed;
- diagnostic devices are appropriately labelled
  e.g. 'for investigational use' or 'for research use only'; and
- no claims are made, through labelling or promotion of the product, that the IVD under investigation is safe and effective.

If a special clinical need can be demonstrated for a new or unusual product prior to registration, the device may be supplied within the provisions of the Clinical Trial or Special Access Schemes of the Act.

If an unregistered kit is being used therapeutically, i.e. to diagnose or to monitor progression or therapy of a disease, this constitutes a clinical use under the Act and application to the TGA for supply under one of the above schemes is required. Details are provided in Chapter 1.24 *Access to Unapproved Therapeutic Devices.*

The supply of an unapproved kit for research use is appropriate if no diagnosis is to be made and the identities of the patients are unknown.

Sponsors are permitted to supply their kits for research purposes prior to the evaluation procedures having been completed. The kits may only be supplied to bona fide research institutes as well as to the designated testing laboratories. Such products cannot be used for diagnostic purposes, i.e. specimens must not be identifiable. No advertising or promotion of the product is permitted. The NCDC requires a notification of the kits used for research purposes; however, this is not a requirement of the TGA.

Changes to Products

The sponsor must notify the TGA of any modifications to approved assays as stipulated in the conditions of ARTG registration. Failure to do so may result in the registration of either the HIV or HCV IVD being cancelled.

Sponsors should notify the CAB of any test kit modification on the*Therapeutic Devices Application* form (see Appendix 2). A processing fee will be required if the modification is a variation that does not result in a new product. An application fee is required if the modification results in a new product, i.e. a test kit that is identified as a separate and distinct product in the market place. Evaluation fees will also be required if the modification requires evaluation. Refer to Appendix 3, *Changes to Therapeutic Devices*.

General Details

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Risk Analysis

Refer to Chapter 2.5 *Risk Analysis*.

Table of Equivalence

Refer to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Commercial and Regulatory History

Regulatory Status in Other Countries

- A list of countries in which the diagnostic kit is marketed, including date of approval is required.
- If an overseas regulatory authority has refused marketing approval, or if the kit has been subject to any bans from sale or supply, product recall or product correction, details of these must be provided to the TGA.

Refer also to Chapter 2.1 *Information Applicable to all Registrable Therapeutic Devices.*

Good Manufacturing Practice

Refer to Chapter 1.19 *Good Manufacturing Practice*.

Reporting Conditions

Refer to Appendix 4, *Conditions — Standard and Specific.*

Postmarket Surveillance

Monitoring

Postmarket monitoring programs will assess data from continuous laboratory monitoring, performance in the field, external quality assurance survey programs such as those run by the Royal College of Pathologists Australasia, overseas reports, and mandatory incident reports supplied by sponsors.

The performance of HIV and HCV test kits will be monitored by the NRL in order to establish batch-to-batch variability and identify kit problems (i.e. outside 2 standard deviations of evaluation performance). If a kit demonstrates a continued unsatisfactory performance that is related to the kit and is not remedied by the manufacturer, the NRL will notify the Conformity Assessment Branch. After due consultation with the sponsor, the registration of the kit may be cancelled if the problem cannot be remedied. Refer also to Chapter 1.6 *Postmarket Compliance Programs.*

Quarantine — For Imported Devices Only

Compliance with the *Quarantine Act (1908)* is a function of the Australian Quarantine and Inspection Service (AQIS) of the Department of Primary Industries and Energy (DPIE). Sponsors are required to obtain an Import Permit for importation of human, animal or plant material. Further information on Quarantine requirements may be obtained by phoning AQIS on 02 6272 4578. Refer also to Chapter 1.4 *Quarantine Requirements (AQIS).*

Samples

The NRL evaluates the technical aspects of HIV and HCV laboratory testing, including evaluation of the accuracy and reliability of the test kits, and monitors the postmarket performance of approved kits. Evaluations may be carried out by laboratories under contract to the NRL, and the TGA may request that kits be provided to NRL to facilitate evaluation. The sponsor must then send the requested samples directly to the NRL.

Performance Testing

Evaluations supervised by the NRL consist of three separate stages. An evaluation may be discontinued at any of the three stages of the evaluation procedure. Sponsors will be advised by the CAB of the reasons for discontinuation and for rejecting the application. Appeal provisions apply for rejected applications. Refer to Chapter 1.21 *Appeals Against Decisions*.

Stage 1: Performance Data

Sponsors are required to provide full details of all clinical trial data, product specifications (as outlined above) and an original printed copy of the current package insert.

Clinical Trial Data

Results and performance data obtained from testing of sera from HIV/HCV infected and uninfected subjects should be submitted.

- Full details are required with clinical status and stage of infection of all infected subjects including a full repertoire of test results for each subject.
- The full names of the clinical sites involved in the trials and a contact name (with telephone and fax number or email address) for each are also necessary.
- Data derived from clinical studies conducted in Australia will be accepted for Stage 1 presentation, provided that full documentation of all results and the clinical status of infected subjects is included.

Data from routine use or evaluations of the kit in other countries may also be included as part of the clinical trial data, provided that the test data are substantiated by supplemental testing.

Following a review of the information presented in Stage 1, the NRL will inform TGA if the product can proceed to Stage 2. If the decision is made not to proceed, the sponsor will be advised by TGA of the reasons for rejection.

Stage 2: Preliminary Trials at the NRL

Products that have successfully completed Stage 1 will progress to the preliminary trials stage conducted at the NRL.

- .During the trials, the products are used to test selected panels of characterised samples.

- Only those products that show satisfactory performance on the NRL in-house panels will be considered for Stage 3. The Stage 2 evaluations may be carried out by laboratories under contract to the NRL. The usual number of tests required for Stage 2 is:
  - screening assays— approx. 500;
  - supplemental assays— approx. 300.

Stage 3: Evaluation

Following a satisfactory performance in Stage 2, the NRL will co-ordinate either an NRL-based or a multicentre evaluation of the product.

- This involves testing samples at the NRL and/or laboratories designated by State and Territory health authorities including Red Cross Blood Transfusion Service Laboratories.
- The timing of the evaluation and the selection of testing sites for the Stage 3 evaluation are arranged by the NRL in collaboration with the testing sites and the sponsor.

The Stage 3 evaluations may be carried out on a contract basis organised by the NRL. The usual number of tests required for Stage 3 is:

- screening assays— approx. 10 000;
- supplemental assays— approx. 2 000.

The actual number of tests and number of testing sites required will be determined by the NRL on a kit by kit basis, taking into account the intended market, instrumentation, ease of use for large scale testing, the volume of sample required and number of samples available.

Design — *Labelling*

Labels (draft or sample) showing the following must be supplied:

- test kit name,
- names of all reagents,
- sponsor's or manufacturer's name and address,
- expiry date, warnings,
- lot/batch number,
- the AUST R number.

Shelf Life

Information on expiry periods and recommended storage conditions for individual reagents in the kit and for the assembled kit should be clearly defined. Lighting conditions and any other special conditions, if applicable, must be specified.

Stability data will be evaluated on a case by case basis.

- 'Accelerated' stability testing cannot replace real time stability studies at the maximum recommended storage temperature for the duration of the nominated shelf-life.
- Real-time stability data on testing carried out at various time intervals at the recommended storage temperature (2–8^{o}C) of at least three production batches in support of the proposed shelf life must be provided.
- If more than one assay result is available for any particular time interval, all results should be quoted, rather than, or in addition to, an average figure.

- In addition to assay for content of active ingredient(s) and degradation products, it is also necessary to monitor the physical properties of the product(s) during storage (e.g. discolouration, precipitation, etc.). Tests will vary depending on the formulation in question.

Shelf life may not be extended until the data have been evaluated by the TGA and a new shelf life is approved. Refer to Appendix 3, *Changes to Therapeutic Devices.*

Product Information / Instructions for Use / Promotional Material

The instruction manual should provide an outline of the principles of the assay, its limitations, instructions for use, warnings and precautions, reagent list and interpretation of results. Copies of labels for the assembled kit and the individual reagent containers, including plates (if appropriate) must be provided.

Manufacturing

Antigen/Antibody/Primer(s) Reagents

It is necessary to provide detailed information on the manufacturing processes for these products as follows.

- Describe the source, strain, subtype and history of the HIV and HCV (whichever is relevant) and the cell line in which the HIV was grown (for viral lysates).
- Describe fully all procedures performed during preparation of each final product.
- Indicate all stages at which samples are taken for testing, if applicable.
- Give details of the production of recombinant or synthetic proteins and peptides, including types of vectors used.
- Provide the specifications of all reagents used in the manufacture of the product (e.g. the composition of all media and solutions).
- If antibody reagent is present, specify whether it is polyclonal or monoclonal and give full details of its production.
- Where processes such as inactivation of viruses are involved, provide data to justify the effectiveness of the chosen procedure.
- If PCR technology is used, provide detailed information on the production of primer(s), probe(s), and the method of detection of amplified product for identification of the target nucleic acid.

Control Serum Reagents

For control serum reagents,

- describe the source and methods of processing and testing.
- For the method of inactivation of HIV and HCV in positive control sera:
  - provide full details of test methods and validation data (e.g. Reverse Transcriptase activity on inactivated anti-HIV sera);
  - HIV positive control sera: must be negative for HbsAg and for anti-HCV antibodies;
  - HCV positive control sera: must be negative for HbsAg and for anti-HIV antibodies.
- For negative control sera:
  - give details on the source, tests and data substantiating the claim that the sera are negative for HBsAg, anti-HIV1, anti-HIV2 and anti-HCV antibodies.

Quality Control Tests

- Include details of the Quality Assurance Program in place for the preparation of viral lysates, purified proteins, recombinant proteins, primers, probes, immunoglobulins, coated plates, etc. Methods used to test the following must be fully described and validated:
  - signal intensity,
  - homogeneity of batches,
  - sensitivity,
  - specificity,
  - antisera panels.
- Samples of reference materials, antigens and special reagents should be made available upon request.

Ch. 2.22 In Vitro Diagnostics — HIV / HCV

Please include this completed checklist with your submission

A tick ✓ indicates information that is to be supplied as part of the submission

Evaluation Categories	General Information Requirements Refer Ch.2.1	Additional Information Required Refer Ch.2.22	Reference Vol/Page
General Details	✓		/
Risk Analysis	✓		/
Commercial and Regulatory History	✓	✓	/
GMP	✓		/
Reporting Conditions	✓		/
Postmarket Surveillance	✓	✓	/
Samples to NRL	✓	✓	/
Quarantine ##	✓	✓	/
Perfomance testing at NRL		✓	/
Design and Construction			/
Materials			/
Labelling	✓		/
Packaging			/
PI/Instructions for Use/PM **	✓	✓	/
Manufacturing		✓	/
Quality Control		✓	/
Sterility			/
Biological Safety/Biocompatibility Testing			/
Preclinical (in vivo)			/
Human Clinical Data			/

should comply with AQIS requirements for imported devices containing human and animal derived material

Product Information/Instructions for Use/Promotional Material

Therapeutic Goods Administration

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