Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Regulatory Guidelines for Biologicals

Part 2 - Regulatory life cycle for biologicals that are included on the Australian Register of Therapeutic Goods

Version 1.0, June 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

Version history

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

Contents

Figures

2.1 General information for sponsors

Part 2 is written primarily for sponsors and manufacturers, and explains the different stages of the regulatory process for biologicals—from making an application through to modification or possible removal of products from the Australian Register of Therapeutic Goods (ARTG). These key stages in the regulatory life cycle are shown in Figure 2.1. Each stage is described in a section within this part of the guidelines as follows:

Section 2.1 General information for sponsors

Section 2.2 Approval for inclusion on the ARTG

Section 2.3 Maintaining an ARTG entry

Section 2.4 Modifying an ARTG entry

Section 2.5 Removing a biological from the ARTG

All biologicals that meet the definition of a therapeutic good must be included on the Australian Register of Therapeutic Goods (ARTG) before they are supplied in, imported to, or exported from Australia, unless they are excluded from Therapeutic Goods Administration (TGA) regulation, are declared to not be a biological, or are exempt and otherwise authorised or approved (such as under the Special Access Scheme).

See Section 1.1 for information about excluded and not included biologicals, Section 1.2.6 and Part 3 for further information about exempt uses of biologicals and Section 1.2 for further information about classification of biologicals on the ARTG

For a biological to be included on the ARTG, sponsors must submit a formal application to the TGA seeking approval to supply their biological in Australia (under Part 3-2A of the *Therapeutic Goods Act 1989* [the TG Act]) and pay the applicable fees. Only a sponsor (or an agent acting on behalf of a sponsor) is able to apply to include a biological on the ARTG.

See Section 2.1.1

The application requirements for each class of biological are set out in Section 2.2 below.

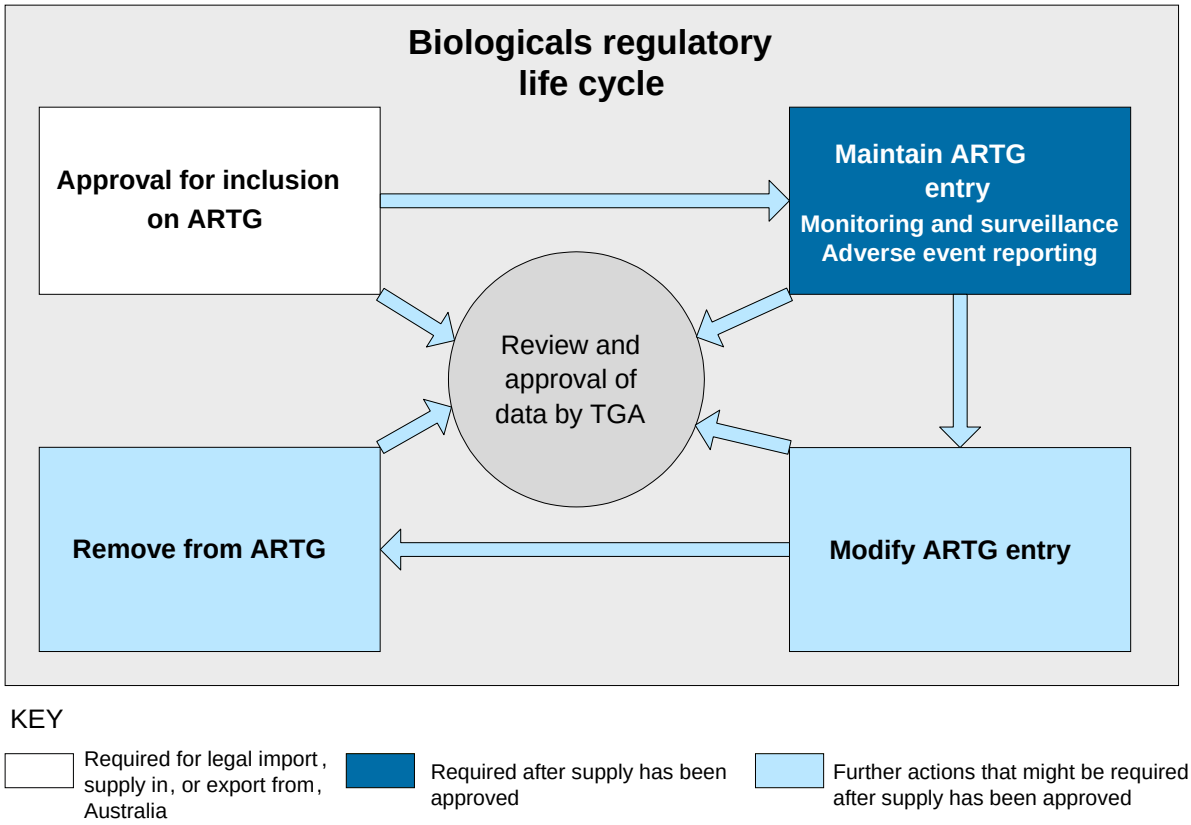
The biological can be included on the ARTG if the TGA determines that the information is satisfactory, the regulatory requirements are met, and (for Class 2, 3 and 4 biologicals) the manufacturer holds an appropriate manufacturing licence (for Australian-based manufacturers) or clearance from the TGA (for overseas-based manufacturers).

Once the TGA considers a biological has satisfied all the requirements for inclusion on the ARTG, it will write to sponsors advising of the date of inclusion on the ARTG and the unique identifying number of the biological. Once the biological is included on the ARTG, the corresponding ARTG certificate is generated by the system and is available for download from the TGA website.

While a biological is listed on the ARTG, the TGA undertakes continuous monitoring and surveillance to collect reports of possible risks and adverse events, and to ensure that all requirements (including current good manufacturing practice and standards) are met.

If necessary, the TGA can request an entry to be modified, suspended or removed from the ARTG altogether (sponsors can also request this for their own products).

Figure 2.1 summarises the regulatory life cycle of biologicals included on the ARTG.



ARTG = Australian Register of Therapeutic Goods; TGA = Therapeutic Goods Administration

Figure 2.1 Regulatory life cycle of biologicals included on the ARTG

2.1.1 How to apply to the Therapeutic Goods Administration

TGA electronic business services

Sponsors must submit applications to the TGA on an approved form. Sponsors will automatically comply with this requirement if they apply electronically, using the TGA's online application form (which is part of the TGA's existing electronic business services—eBS). The system will incorporate an internal work management system to support evaluation of biologicals and for biologicals to be included on the ARTG.

Sponsors can also use this electronic application system to vary existing entries on the ARTG.

All manufacturers (including manufacturers of Class 1 biologicals) and sponsors need to be included on the TGA's client database, which is also available through eBS. Sponsors and manufacturers can make arrangements to be included on this database via the eBS website.

Supporting information

For Class 2, 3 and 4 applications, dossiers and any other supporting information must be supplied to the TGA in hard copy, and also in an editable electronic format. Dossiers supporting an application should be posted or couriered to:

Postal address
Therapeutic Goods Administration
PO Box 100, Woden ACT 2606, Australia

Street address (for courier deliveries)
Therapeutic Goods Administration
136 Narrabundah Lane, Symonston ACT 2609, Australia

The rules governing when separate ARTG entries are required are described in Section 1.2.5

Each application is generally required to be supported by its own dossier unless there are enough common data relating to multiple products for a single evaluation of the dossier. In those instances, a single dossier may result in several separate ARTG entries. This should be discussed with the TGA before application.

Different principal manufacturers cannot make a joint submission through a sponsor to include a biological on the ARTG. Separate submissions are required, even if the same sponsor is acting on behalf of each principal manufacturer. Australian-based manufacturers can also be sponsors.

2.1.2 Fees

The TGA recovers the full cost of its regulatory activities, under the TG Regulations and the *Therapeutic Goods (Charges) Act 1989*, through fees and charges. The TGA recognises that public institutions (such as hospitals) undertake a significant proportion of the manufacture of biologicals. Many of these organisations have been exempt from fees and charges in the past.

Cost recovery is the recovery of some or all of the costs of a particular activity. Australian Government cost-recovery charges fall into two broad categories: fees for goods and services, and cost-recovery taxes (primarily levies, but also excises and customs duties).

The types of fees and charges collected by the TGA are aligned with those collected for other therapeutic goods and include:

- application fee for including a new, or modifying an existing, ARTG entry (all classes)
- application fee for a cGMP licence (Class 2, 3 and 4 biologicals)
- evaluation fee for evaluating the product dossier for new ARTG entries or modifying existing ARTG entries (Class 2, 3 and 4 biologicals)
- manufacturing audit fees for biologicals requiring a cGMP licence (Class 2, 3 and 4 biologicals)

- fees for clinical trial applications
- annual charge for maintaining each ARTG entry (all classes).

An evaluation fee is payable for every dossier evaluated by the TGA. Fees are subject to annual revision, and as such Schedule 9A of the TG Regulations and Regulation 3 of the TG (Charges) Regulations should be consulted for current information.

See the *Cost recovery impact statement for biologicals* (available on the TGA website) for further information about cost recovery and how fees are set

When do fees have to be paid?

The application invoice is raised at the time of successful electronic submission of the application. Application fees are payable within 14 days of the date of invoice. Following payment of the fee, the TGA will screen the application and dossier (or certification requirements for a Class 1 biological) and determine whether to proceed to evaluation (for Class 2, 3 and 4 biologicals).

. The evaluation invoice is raised once the application is accepted for evaluation. The evaluation invoice is payable within 28 days of the date of invoice.

See Section 2.1.3 for further details about the timing of fee payments

Do audit fees apply to every manufacturing site?

For manufacturers with more than one site, each manufacturing site must undergo a successful audit to be included on a manufacturing licence. A fee applies to each audit site; however, sites that are not the primary manufacturing site incur a reduced fee.

See the *Therapeutic goods (multi-site manufacturing licences) guidelines 2010* (available on the TGA website) for information on manufacturing sites for blood, blood components, plasma, haematopoietic progenitor cells and human tissue

Will the orphan drug scheme apply to biologicals?

The orphan drug scheme (currently in operation for medicines) will not apply to biologicals, because the costs of regulation are fully cost recovered from the regulated entities. This is consistent with the recommendation in 2006 by Australian Health Ministers that the costs of regulation are to be fully recovered from the regulated entities.

2.1.3 Timelines

Class 1 applications

The TG Act and the Therapeutic Goods Regulations (1990) (TG Regulations) do not currently provide a timeline for Class 1 applications.

See Section 2.2.3 for details about Class 1 applications

Class 2, 3 and 4 applications

The application process for Class 2, 3 and 4 biologicals starts when the sponsor submits an application and application fee using the electronic application system (see Section 2.1.1). The electronic application system provides for the application fee invoice to be raised and paid within 14 days.

In order for an application to be considered effective, the following requirements must be addressed:

- The eBS application form is completed
- Accompanying documents are received by the TGA, including the dossier and any other documents requested or that are pertinent to the application
- If required, samples of the biological must be provided
- The application fee has been received

The number of days allowed for the processing of the initial application for Class 2, 3 and 4 applications, and the evaluation of dossiers, is set out in the TG Regulations. All numbers of days are calendar days (not working days).

The TGA must complete the processing of the application within 40 days and notify the sponsor of whether the application is accepted or rejected.

The 40 days starts from the day after the application fee is received.

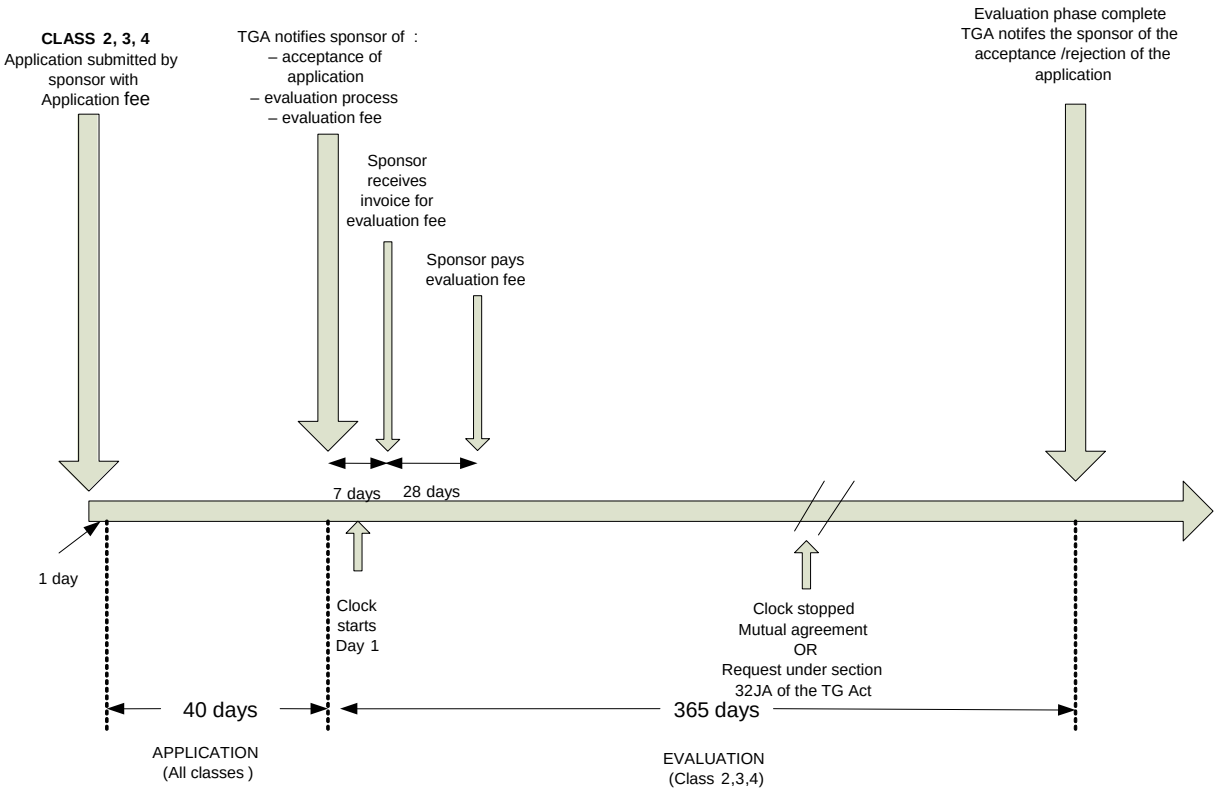
At the same time as notifying the sponsor that the application has been accepted, the TGA will also advise sponsors about the evaluation process and the evaluation fee. An invoice for the evaluation fee will be sent to sponsors within seven days acceptance of the application. Sponsors have 28 days to pay the evaluation fee in full. There is no provision for application or evaluation fees to be paid in instalments.

The evaluation process must be completed within 365 days of the TGA sending the letter advising of the acceptance of the application and advising of the evaluation process. This applies to either an application for a new entry on the ARTG or a variation of an existing entry. The clock starts (i.e. day 1 starts) the day after the TGA notifies the applicant.

Although a maximum of 365 days is allowed for evaluation of a dossier (for Class 2, 3 and 4 biologicals), the actual time taken to approve a biological can vary considerably and is influenced by the nature of the issues arising during the evaluation process, as well as whether consideration by the Advisory Committee on Biologicals is required. This time consists of time spent by the TGA evaluating the product, and the time spent with the sponsor or manufacturer clarifying questions raised by the TGA. While the TGA and industry work together to reduce the total evaluation time, the total time depends heavily on the quality of the submission that is initially received, and on the preparedness of the sponsor to work with the TGA.

If an issue arises during the evaluation, under section 32JA of the TG Act, the TGA can also request additional information from the sponsor. The clock is stopped from the time that the TGA makes the section 32JA request until the time that the sponsor submits the requested information.

In other circumstances, the clock can be stopped by mutual agreement between the sponsor and the TGA and restarted when the issue has been resolved.



TG Act = *Therapeutic Goods Act 1989*; TGA = Therapeutic Goods Administration
Note: All days are calendar days

Figure 2.2 Time line for application and evaluation process for inclusion of biologicals on the Australian Register of Therapeutic Goods

See Section 2.2.4 for further details about Class 2, 3 and 4 applications

2.2 Approval for inclusion on the Australian Register of Therapeutic Goods

This section provides sponsors and manufacturers with specific information on how to lodge their application, the fees and time lines, and the different types of applications that can be lodged.

Applications for inclusion on the ARTG need to be submitted electronically via the TGA's electronic business system. However, dossiers must be posted to the TGA.

See Section 2.1.1 for further information about electronic submission of applications

2.2.1 Overview of the process

For a biological to be included in the biologicals section of the ARTG, sponsors must submit a formal application to the TGA seeking approval to supply their biological in Australia (under Part 3-2A of the TG Act) and pay the applicable fees. Only a sponsor can apply to include a biological on the ARTG.

As discussed in Section 1.4, the TGA uses a risk-management approach to determine the level of data required for biologicals (and all therapeutic goods) to assess whether it is appropriate to include them on the ARTG. Therefore, the data requirements for each class of biological vary.

The dossier requirements for each class of biological are described in this part of the guidelines; further information, templates and checklists are provided in Appendix 1-3 of this guidance.

If the information is satisfactory, the regulatory requirements are met and (for Class 2, 3 and 4) the manufacturer holds an appropriate TGA manufacturing licence (or overseas equivalent), the biological is included on the ARTG with a unique identifying number, and a biologicals certificate is generated and can be downloaded by the sponsor or manufacturer.

2.2.2 Classification of a biological

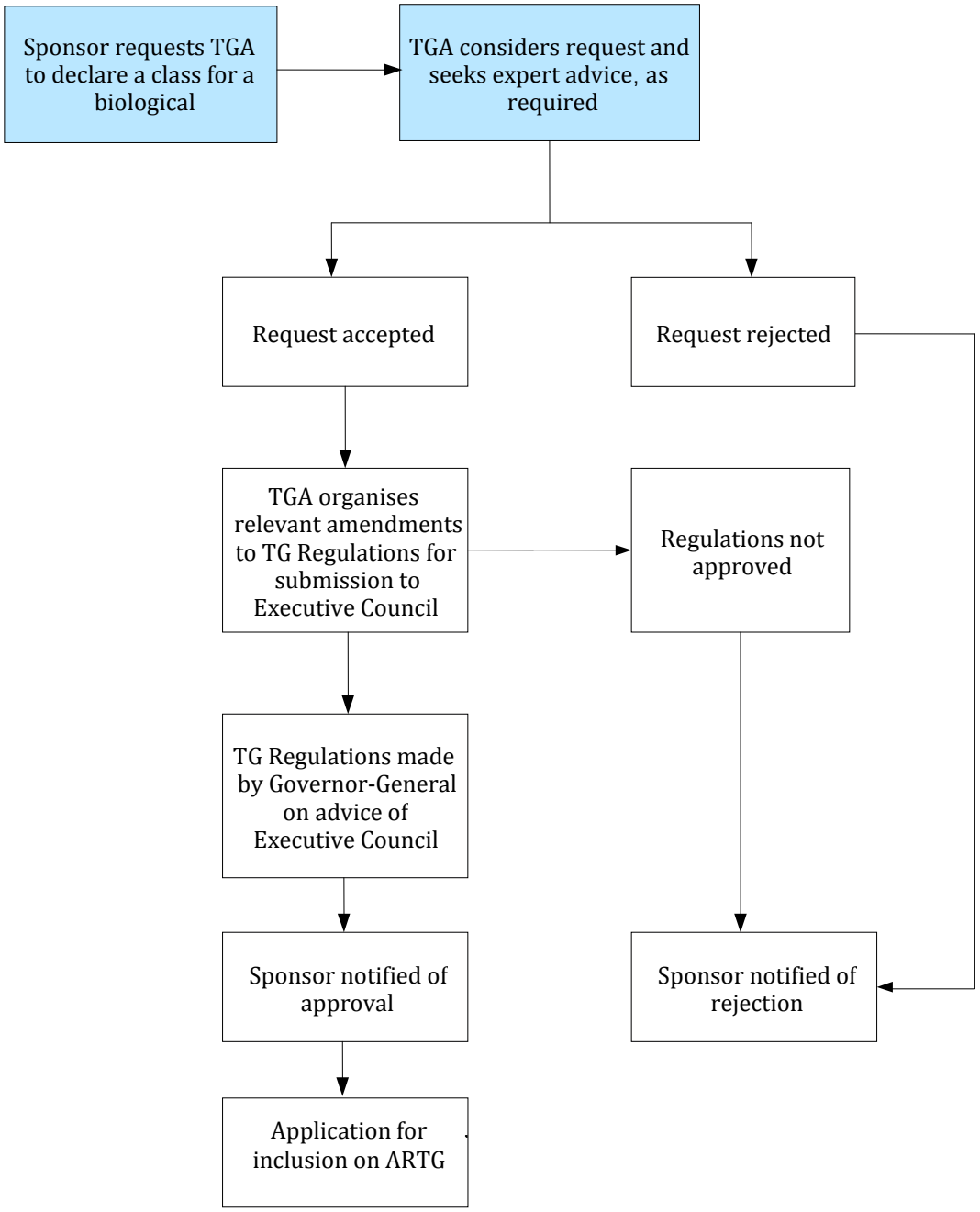
There are two methods of classifying a biological:

- classification based on method of preparation and use of the biological.
- classification based on inclusion in Schedule 16 of the TG Regulations

Section 1.2 provides details about the classification of biologicals

Inclusion in Schedule 16 of the Therapeutic Goods Regulations

The process for classification of a biological by inclusion in Schedule 16 of the TG Regulations is shown in Figure 2.3.



ARTG = Australian Register of Therapeutic Goods; TGA = Therapeutic Goods Administration; TG Regulations = Therapeutic Goods Regulations (1990)

Figure 2.3 Process for declaring a biological class under Schedule 16 of the TG Regulations

The sponsor should write to the TGA to request and justify -that the class of the biological is declared and included in Schedule 16.

See Section 1.5 for further information about Schedule 16

The TGA may forward the application to the Advisory Committee on Biologicals for advice, as required. If the request is accepted, the TGA will make the necessary arrangements for the biological to be included in the new Schedule 16 of the TG Regulations (see Figure 2.1).

Sponsors seeking to classify a biological using this method need to take into account the timeframes involved in this process, because sponsors cannot submit an application until the TG Regulations have been amended and a class for the biological has been declared.

Once the TGA has made a decision to declare a particular biological as Class 1, 2, 3 or 4, and the TG Regulations have been amended accordingly by the Governor-General, the application (all classes) and the evaluation process (Class 2, 3 and 4 only) followed will be exactly the same as those that apply to that class of the biological determined based on method of preparation and use.

Classification based on the preparation and use of the biological

As described in Section 1.2, the TG Regulations define four classes of biologicals based on their preparation (level of manipulation) and use (homologous or nonhomologous). If sponsors are not seeking to have their biological included in Schedule 16 of the TG Regulations, they should seek advice from the TGA on the classification of the biological before they submit their application (see Section 2.2.3, step 1).

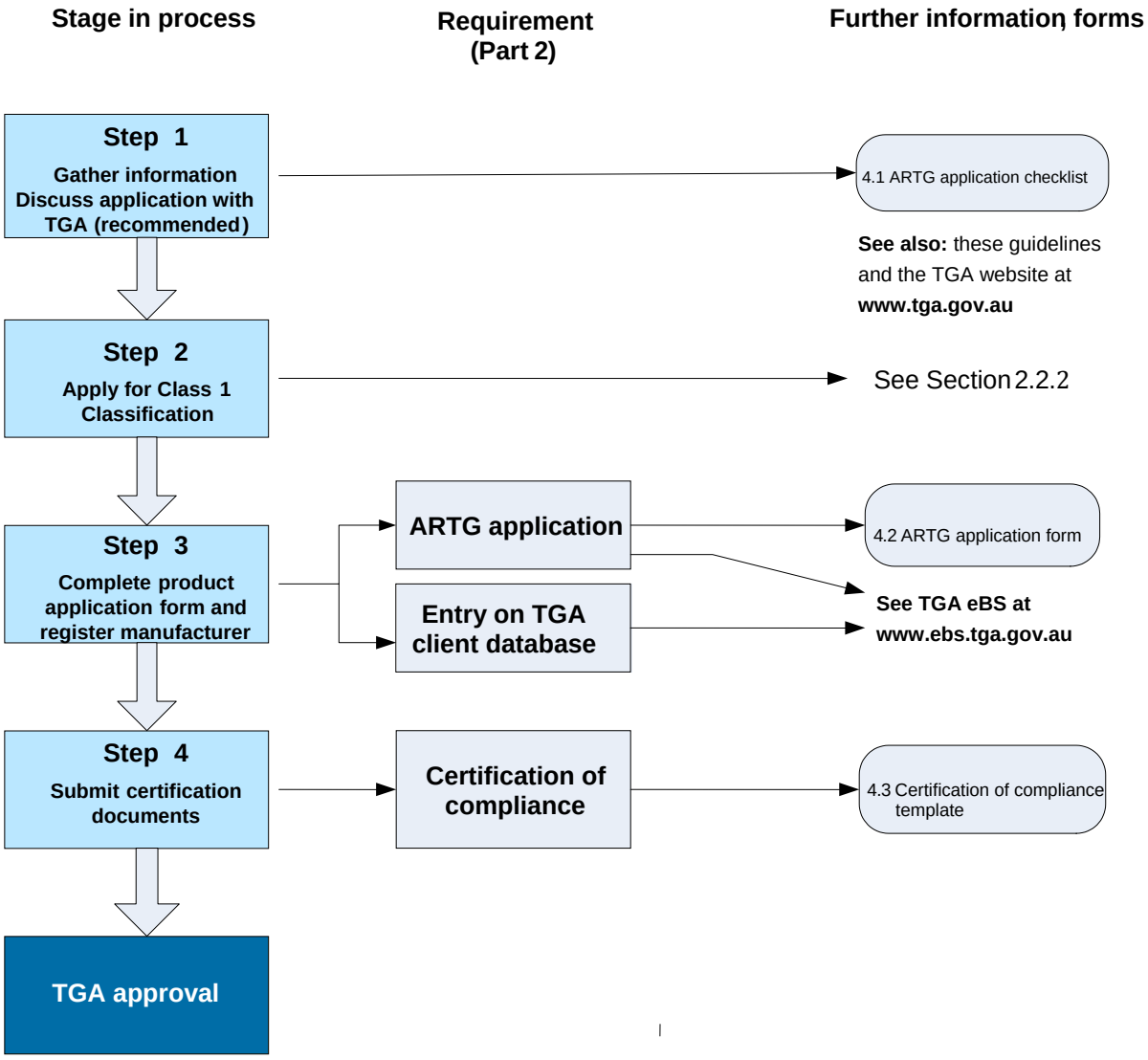
Important advice for sponsors

The Therapeutic Goods Administration (TGA) strongly recommends that sponsors contact the TGA to discuss applications before lodgement. This is because TGA endorsement of the classification of a biological on application is critical for the application being accepted. The TGA application screening process will review, among other things, whether the proposed classification is appropriate.

2.2.3 Applying for inclusion of a Class 1 biological

Clause 32DA of the TG Act describes the application process for inclusion of a Class 1 biological on the ARTG. The overall application process is shown in Figure 2.4. Each step is described in this section.

Examples of the forms that accompany each of these stages are available on the TGA website



ARTG = Australian Register of Therapeutic Goods; eBS = electronic business service; TGA = Therapeutic Goods Administration

Figure 2.4 Application process for inclusion of a Class 1 biological on the Australian Register of Therapeutic Goods

Step 1—Collect information and discuss your application with the TGA

Sponsors should read these guidelines for further information about the Biologicals Regulatory Framework, and the application process for inclusion of a biological on the ARTG. General information about the TGA and the regulation of therapeutic goods is on the TGA website.

Sponsors are strongly recommended to contact the TGA to discuss their application—in particular, the classification of their biological—before lodging their application form. The application screening process

begins with a review of this classification, and applications for biologicals that have been inappropriately classified will be returned. Only applications for correctly classed biologicals can be lodged.

Step 2—Apply for Class 1 classification for the biological

For a Class 1 application, the biological must be declared as a Class 1 biological and listed in Schedule 16 of the TG Regulations before an application can be lodged for inclusion on the ARTG.

Section 2.2.2 describes how to apply for inclusion in Schedule 16

The TGA will seek expert advice if required. Once the TGA has decided to declare a particular biological as Class 1, it will complete the required approval processes, including listing the biological in Schedule 16 of the TG Regulations. The application for inclusion on the ARTG cannot proceed until this step is complete.

Step 3—Complete the application form and register the manufacturer

When they are ready to start the application process, sponsors should complete and submit the application form on eBS.

See Section 2.1.1 for further information about eBS

The form must be accompanied by:

- the application fee
- a statement as described in Step 3, below.

Applications can be submitted electronically. The eBS system will allow the certification form for a Class 1 biological to be downloaded and attached to the application form.

Although a manufacturer's licence is not required for Class 1 biologicals, the manufacturer must be included on TGA's client database, which is available through eBS.

See Section 2.1.1 for further information about the client database

Step 4—Submit written certification

Sponsors who are applying to have a Class 1 biological included on the ARTG must submit a written certification confirming that the biological:

- is Class 1
- is safe for the purposes for which it is to be used
- conforms to every standard (if any) applicable to it
- complies with every requirement (if any) relating to advertising applicable under Parts 5-1 of the TG Act or under the TG Regulations
- complies with all prescribed quality or safety criteria that are applicable to it
- does not contain substances that are prohibited imports for the purposes of the *Customs Act 1901*.

Such certification will be required even where a biological is declared through inclusion in Schedule 16 of the TG Regulations.

The relevant form to meet the above certification requirement is available for download from eBS. Once completed and signed, the form can be electronically returned to the TGA; however, the original signed hard copy needs to be posted to the TGA.

See Section 2.1.1 for the postal address of the TGA

TGA approval

If the documentation is complete and approved by the TGA, the Class 1 biological will then be entered on the ARTG, assigned a unique biological identifier and automatically awarded a biological certificate (which can be accessed via the eBS website).

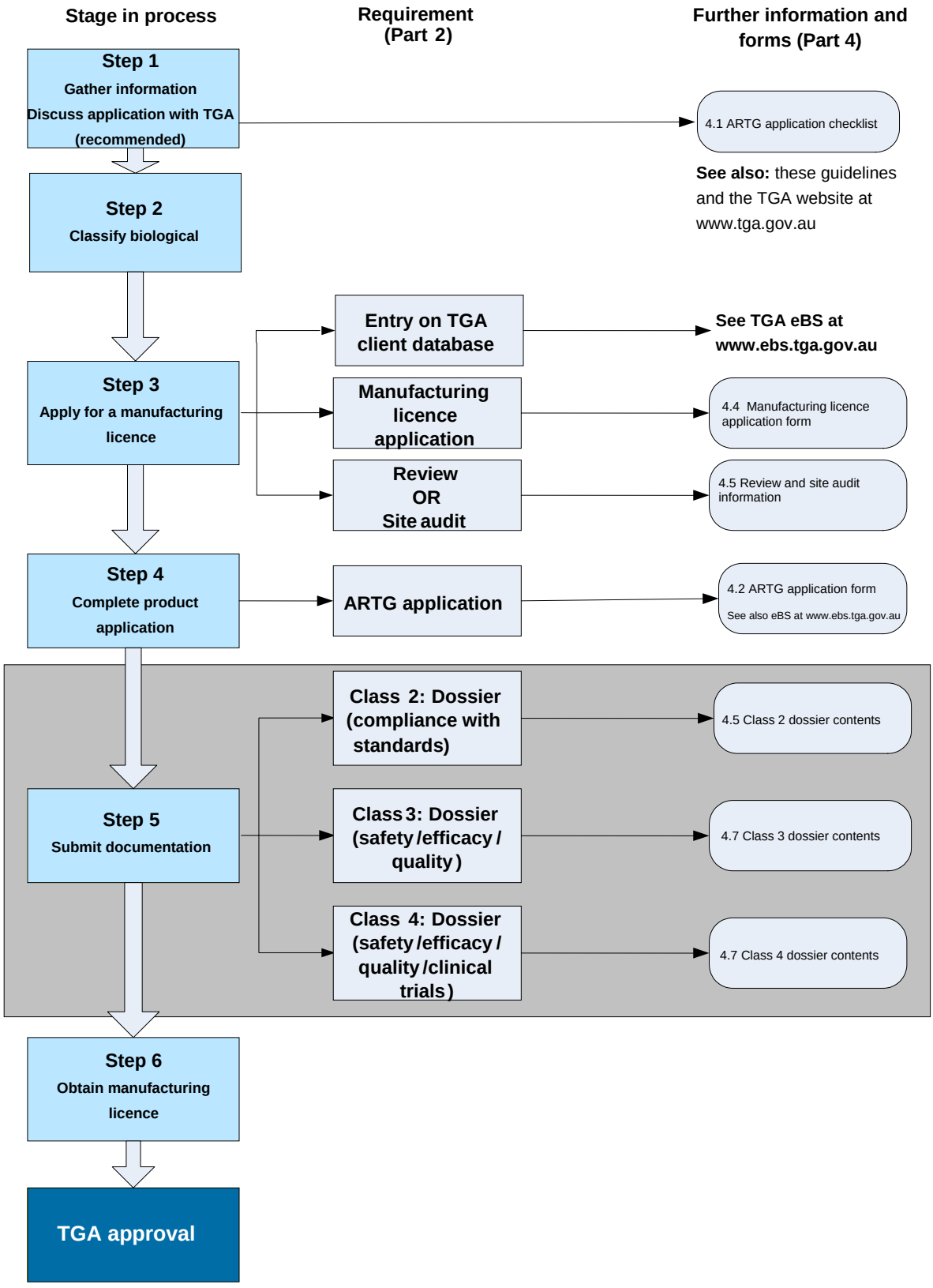
2.2.4 Applying for inclusion of a Class 2, 3 or 4 biological

The overall application process for inclusion of Class 2, 3 and 4 biologicals on the ARTG is shown in Figure 2.3. Each step is described in the remainder of this section.

Examples of the forms that accompany each of these stages are available on the TGA website

Important note about application for a manufacturing licence

A key point is that a manufacturing licence is not required when the application is lodged, but a current licence is required for the biological to be included on the Australian Register of Therapeutic Goods. This means that a manufacturing licence can be applied for at any step (1–4), as long as it is finalised by the time the evaluation process has been completed. However, the best time to apply for a licence is during steps 2 and 3—applying during step 1 (the information-gathering stage) is likely to be too early, and applying after step 3 (when the Therapeutic Goods Administration is ready to approve or reject the application) is too late.



ARTG = Australian Register of Therapeutic Goods; eBS = electronic business service; TGA = Therapeutic Goods Administration

Figure 2.5 Application process for inclusion of a Class 2–Class 4 biological on the Australian Register of Therapeutic Goods

Step 1—Collect information and discuss the application with the TGA

Sponsors should read these guidelines for further information about the Biologicals Regulatory Framework, and application process for inclusion of a biological on the ARTG. General information about the TGA, the regulation of therapeutic goods in general, and the regulation of biologicals, in particular, is provided on the TGA website.

Sponsors are strongly recommended to contact the TGA to discuss their application—in particular, the classification of their biological—before lodging their application form. The application screening process begins with a review of this classification, and applications for biologicals that have been inappropriately classified will be returned. Only applications for correctly classed biologicals can be lodged.

Step 2—Classify the biological

Class 2, 3 or 4 biologicals can be classified either by application for inclusion in Schedule 16 of the TG Regulations, or based on method of preparation and use of the biological.

See Section 2.2.2 for further information on classifying a biological

The application for inclusion on the ARTG cannot proceed until this step is complete.

Step 3—Apply for a manufacturing licence

A Class 2, 3 or 4 biological will only be approved for inclusion on the ARTG if the manufacturer of the biological holds a current manufacturing licence.

While an application can be submitted before a current manufacturing licence has been obtained, the licence must be obtained before the biological is included on the ARTG. Manufacturers who already have a licence should check that it will still be current by the time the entry is included on the ARTG.

Further information on manufacturing licences is available on the TGA website

Important information about applying for a manufacturer's licence

Because the manufacturing licence is not required when the application is lodged, it can be applied for at any step (1–4), as long as it is finalised by the time the evaluation process has been completed. However, the best time to apply for a licence is during steps 2 and 3—applying during step 1 (the information-gathering stage) is likely to be too early, and applying after step 4 (when the Therapeutic Goods Administration is ready to approve or reject the application) is too late.

The manufacturer must also be included on the TGA's client database, which is available through eBS.

See Section 2.1.1 for further information about the client database

Step 4—Complete the application form

When they are ready to start the application process, sponsors should complete and submit the application form on eBS.

See Section 2.1.1 for further information about eBS

The application form must be submitted electronically; the dossier must be posted to the TGA.

See Section 2.1.1 for the postal address of the TGA

The TG Regulations also give the TGA (on behalf of the Secretary) leeway to select the most appropriate form for each biological. The Secretary will notify the sponsor if a different application form is needed.

Step 5—Submit documentation for evaluation by the TGA

The documents that are needed for each class of biological are listed below by class:

- evidence of currency of manufacturing licence
- a dossier containing evidence supporting the intended use and quality aspects of the manufacturing process (Class 2)
- a dossier containing clinical and nonclinical data showing the safety, efficacy and quality of the biological (Class 3 and 4).

Consistent with similar provisions in the TG Act for other therapeutic goods, the applicant may be asked to submit a reasonable number of samples of the biological.

Class 2 biologicals

Sponsors making an application for a Class 2 biological are required to demonstrate compliance with:

- **Manufacturing requirements—**the TGA requires evidence of compliance for all the steps in the manufacturing process (as defined by the TGA Office of Manufacturing Quality) by the facility or facilities in which the tissue will be manufactured. To show that the biological meets the relevant manufacturing requirements for Class 2, manufacturers must have a manufacturing licence issued by the TGA before the ARTG entry is made (see steps 3 and 6 for further details).

See the TGA Office of Manufacturing Quality website for further information.

- **Relevant standards** for each tissue type. To provide evidence that the biological meets all the relevant standards, sponsors of Class 2 biologicals must submit a hard copy of a dossier with information showing how the product complies with each applicable standard

Further information on the preparation and contents of a dossier for a Class 2 biological is available in ARGB Appendix 1 – Guidelines on Class 2 Biological dossier requirements.

Class 3 biologicals

Sponsors making an application for a Class 3 biological are required to:

- **Manufacturing requirements—**the TGA requires evidence of compliance for all the steps in the manufacturing process (as defined by the TGA Office of Manufacturing Quality) by the facility or facilities in which the tissue will be manufactured. To show that the biological meets the relevant manufacturing requirements for Class 3, manufacturers must have a manufacturing licence issued by the TGA before the ARTG entry is made (see steps 3 and 6 for further details)

See the TGA Office of Manufacturing Quality website for further information.

- Demonstrate the biological's **safety, efficacy and quality**—this requires the sponsor to submit a dossier to the TGA. To provide evidence that the biological meets all the relevant standards, and to demonstrate safety and efficacy, sponsors of Class 3 biologicals must submit a hard copy of a dossier that demonstrates the safety, efficacy and quality of the biological through provision of data

Further information on the preparation and contents of a dossier for a Class 3 biological is available in ARGB Appendix 2 – Guidelines on Class 3 Biological dossier requirements.

Class 4 biologicals

Sponsors making an application for a Class 4 biological are required to:

- **Manufacturing requirements—**the TGA requires evidence of compliance for all the steps in the manufacturing process (as defined by the TGA Office of Manufacturing Quality) by the facility or facilities in which the tissue will be manufactured. To show that the biological meets the relevant manufacturing requirements for Class 4, manufacturers must have a manufacturing licence issued by the TGA before the ARTG entry is made (see steps 3 and 6 for further details)

See the TGA Office of Manufacturing Quality website for further information.

- Demonstrate the biological's **safety, efficacy and quality**—this requires the sponsor to submit a dossier to the TGA. To provide evidence that the biological meets all the relevant standards, and to demonstrate safety and efficacy, sponsors of Class 4 biologicals must submit a hard copy of a dossier that demonstrates the safety, efficacy and quality of the biological through provision of data. This includes information on the conformance of the product to applicable standards (as for Class 2)
- provide the additional relevant clinical data and analysis (included in the dossier)

Further information on the preparation and contents of a dossier for a Class 4 biological is available in ARGB Appendix 3 – Guidelines on Class 4 Biological dossier requirements.

TGA evaluation

In each case (Class 2, 3 or 4), the documentation submitted will be evaluated by the TGA to ensure that:

- the quality, safety and efficacy of the biological have been satisfactorily established for the proposed use(s)
- the presentation of the biological is acceptable
- the biological conforms to any standard applicable to it
- if a step in the manufacture of the biological has been carried out outside Australia and the biological is not exempt from the operation of Part 3-3 of the TG Act—that the manufacturing and quality control procedures used in the step are acceptable
- the biological complies with every requirement (if any) relating to advertising
- the biological does not contain substances that are prohibited imports for the purposes of the *Customs Act 1901*
- all the manufacturers of the biological are nominated as manufacturers of the biological in the application
- other matters (if any) that the Secretary considers relevant.

Step 6—Obtain the manufacturing licence

Manufacturers who do not already have a licence and who applied for a manufacturing licence at step 3, above, should now ensure that they obtain a licence while the TGA is evaluating the submitted dossier of information.

TGA approval

If, after the evaluation, the TGA considers that it is appropriate to include the biological on the ARTG, and the application fees are paid in full, the biological will be awarded a biological certificate, assigned a unique biological identifier, and entered on the ARTG.

Biological number

The biological number will be any combination of numbers and either or both of letters and symbols.

Note: The number assigned is known as the 'biological number' of the biological.

Certificate

The biological certificate will:

- specify the biological number of the biological
- specify the day on which the biological is included in the ARTG .

Duration of inclusion in the ARTG

The biological will remain included in the ARTG until the TGA (on behalf of the Secretary) cancels the entry.

2.2.5 Other application requirements

Separate ARTG entries

The TG Regulations describe the circumstances in which biologicals may be defined as 'separate and distinct' and require separate ARTG entries.

See Section 1.2.5 for details about the requirements for separate and distinct biologicals and separate ARTG entries

In some circumstances, Class 3 and Class 4 biologicals may be defined as 'separate and distinct' products, but the TGA will still allow these to be grouped within a single ARTG entry. These specific circumstances will be explained in a therapeutic goods order. There is no provision in the legislation for the creation of such an order at this stage, but amendment to provide for such an order will be included in future. In the meantime, sponsors should contact the TGA if such circumstances arise.

Therapeutic kits, systems or procedure packs containing biologicals

See Section 1.1.3 for information on kits, systems and procedures packs

Export-only products

Sponsors intending to apply to register a biological for export only should clearly state this in their application. This is because Class 3 and Class 4 export-only biologicals have reduced premarket evaluation requirements: the premarket evaluation process for Class 3 and 4 export-only biologicals is the same as for Class 2 biologicals that are intended for domestic supply. Further evaluation may be required by the importing country.

2.3 Maintaining an entry on the Australian Register of Therapeutic Goods

A biological remains on the ARTG (as long as the annual fees for retaining the entry on the ARTG are paid) until the Secretary cancels the entry of the biological from the ARTG.

2.3.1 Monitoring and surveillance

[Still to be completed]

2.3.2 Adverse event reporting

Adverse event reporting for biologicals are based on existing processes established within the TGA. Sponsors are required to monitor and keep records of all adverse events, including mandatory reporting of serious adverse events within statutory timeframes. Medical practitioners, patients, and others are encouraged to report any incidents/adverse events to the TGA. The TGA investigates and responds to adverse events as appropriate.

2.3.3 Exceptional release

The exceptional release provisions of the TG Act and TG Regulations allow the use of biologicals that are included in the ARTG but do not conform to the standards required or current code of Good Manufacturing Practice (cGMP). Part 5A of the TG Regulations describes the circumstances for import, export or supply (exceptional release) of such a nonconforming biological. For example, a stem cell product may not have completed all required infectious disease screening, but is the only unit of this product available for treating a patient with a life-threatening disease. In such a case, with informed consent given, the product can be used for treatment, even though it does not conform with the applicable standards. This arrangement is unique to biologicals and does not exist for other therapeutic goods.

See Section 1.2.6 for further background information about exceptional release

Exceptional release recognises the uniqueness and potential scarcity of correctly matched biologicals, and enables the use of products that would have otherwise been discarded for not conforming.

The TG Regulations allow exceptional release of a biological when the following conditions are all met:

- The patient is seriously ill and has been clinically assessed by the treating medical practitioner to require the biological urgently to treat a serious condition.
- A biological that is included on the ARTG and conforms with the applicable manufacturing requirements and standards is not available or not available within the time necessary for treatment to occur.
  OR
  A biological is available that is included on the ARTG but it does not conform with the relevant standards specified under section 10 of the TG Act and/or the relevant manufacturing principles as specified under section 36 of the TG Act.
- No other approved therapeutic good would be suitable.
- In light of the above and given the clinical situation, the biological is assessed by the treating medical practitioner as the most suitable treatment for the patient.

- The biological is to be used only for the treatment of one patient.

Before the biological can be supplied, the sponsor must receive from the treating medical practitioner a copy of:

- a document signed by the treating medical practitioner providing an explanation of the situation and the proposal to use the nonconforming biological, certifying that the patient or guardian has been fully informed of the likely risks and benefits from the use of the biological, and that the biological is nonconforming with required standards and/or manufacturing principles
- the written informed consent received from the patient or their guardian completed before the biological is used.

If the sponsor agrees to release the biological for the use sought, where the above requirements are met, the sponsor must make a written record of the decision and give a copy to the treating medical practitioner.

The sponsor must submit a notification of supply of the biological to the TGA on a TGA-approved form. This sponsor notification must occur within 28 days after the exceptional release and must include:

- a copy of the approval of release from the medical or scientific director of the sponsor's facility from where the biological will be supplied
- a copy of the informed consent statement from the patient or guardian (or statement from the treating medical practitioner explaining why the patient or guardian cannot give consent).

Within 28 days of receipt of the notification and any further information sought by the Secretary, the Secretary must provide written acknowledgment of receipt of the notification.

If a sponsor decides to release a nonconforming biological, manufacturers will be required to provide to the TGA within six months a report of all products released under the exceptional release arrangements. This report must include:

- date of release
- product identification
- name and address of the medical facility where supply occurred, or the name of the medical practitioner to whom it was released
- patient identification (initials, sex, date of birth).

Sponsors and medical practitioners involved in providing nonconforming biologicals under these exceptional release provisions must also report any adverse events to the TGA within six months.

2.4 Modifying an entry on the Australian Register of Therapeutic Goods

Sponsors can vary their entry on the ARTG at any time. There are two types of variations to ARTG entries: those that require prior TGA approval, and those that can be made by simply notifying the TGA of the change. The latter process allows the following variations to be made:

- minor changes to product or trial data
- change of manufacturer details or facility details for manufacturers already holding a TGA manufacturing licence.

See Table 2.1 for the list of fees

Changes that require prior TGA approval are classified as either major changes or minor changes. Major variations include:

- a change requiring submission and evaluation of clinical data
- extension of an indication
- a new strength
- a new route of administration
- a change in the intended patient group
- a change in dosage.

Minor variations include:

- a change requiring evaluation of quality and manufacturing information
- a new manufacturing site
- a change in specification
- a change in container.

All variations (major, minor and notifiable) are recorded on the ARTG and require a flat application fee, irrespective of class, to be paid by the sponsor upon application. As for premarket applications, the electronic application system will generate an invoice upon completion of the application.

See Section 2.1 for further information about the electronic application system and fees

Sponsors will need to submit a dossier to the TGA to support any variations for Class 2, 3 and 4 products (including clinical data, if required). Notifiable variations will also need to be supported by data to justify that the variation does not require TGA approval. Evaluation fees are also applicable for TGA evaluation of these submissions.

See Table 2.1 for a list of evaluation fees applicable for variations

The nature of the variation and the classification of the biological may result in a new ARTG entry being required. Therefore, the process for including a new biological on the ARTG must be followed, and the application and evaluation fees for a new ARTG entry will apply.

As for new ARTG entries, the eBS application form must be used.

2.5 Removing a biological from the Australian Register of Therapeutic Goods

Only the TGA can suspend or remove an entry from the ARTG. The TGA may do so on its own initiative or at the request of the sponsor.

Sponsors must submit a request for suspension or cancellation to the TGA in writing. There are no forms or templates for this (and it cannot be done electronically).

Where the suspension or cancellation is not initiated by a sponsor, the TGA will notify the sponsor of the decision, the proposed date of effect, and the reasons for the decision.

No fees are incurred for suspending or cancelling an ARTG entry. However, application fees (and evaluation fees, if applicable) will be charged to restore a previously included entry where the product entry was cancelled.

2.6 References

Resource	URL
TGA website	http://www.tga.gov.au/
eBusiness information	http://www.tga.gov.au/about/ebs.htm
Manufacturing information	http://www.tga.gov.au/industry/manuf.htm
TGA Office of Manufacturing Quality	http://www.tga.gov.au/about/tga-structure-omq.htm

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