Dossier requirements for Class 2, 3 and 4 biologicals

Australian Regulatory Guidelines for Biologicals (ARGB)

Version 1.1, November 2021
Contents

Introduction ........................................................................................................... 5

Format of biologicals dossier ................................................................. 5
Content of biologicals dossier ................................................................. 5
Guidance on applicable standards .......................................................... 5
International reference and guidance documents ................................................. 6
Dossier checklist ........................................................................................... 6
Contacting TGA ............................................................................................ 6

Dossier structure ......................................................................................... 7

eCTD dossier structure .................................................................................. 7
TGA biologicals dossier structure .................................................................. 7

Technical requirements .................................................................................. 9

1. Introduction .................................................................................................... 9

1.1 Table of Contents ....................................................................................... 9

2 Scope .............................................................................................................. 10

3 Risk management ......................................................................................... 11

4. Quality and manufacturing aspects ......................................................... 12

4.1 Biological starting material ................................................................. 12
4.2 Manufacturing process .......................................................................... 15
4.3 Characterisation ...................................................................................... 18
4.4 Control of finished product ................................................................. 19
4.5 Storage and stability .............................................................................. 21
4.6 Product development ............................................................................ 22
4.7 Labelling and release documentation .................................................. 22
4.8 Transportation ......................................................................................... 23

5. Intended use – Class 2 biologicals only ...................................................... 24

How intended use differs from indication .................................................... 24
Justifying efficacy in your supporting statement ........................................ 24
Completing the biologicals application form .............................................. 24
5.1 Risk Management Plan – upon request only for Class 2 biologicals---- 24

5. Non-clinical development – Class 3 & 4 biologicals only ...................... 25

Purpose of non-clinical development ........................................................... 25
Required information .................................................................................... 25
Recommended tests....................................................................................... 25
Supporting publications ------------------------------------------------------------- 25
5.1 Biological dynamics and kinetics----------------------------------------------- 26
5.2 Toxicology -------------------------------------------------------------------- 27

6. Clinical development – Class 3 & 4 biologicals only__________________________ 28
   Background ---------------------------------------------------------------------- 28
   Required information ------------------------------------------------------------- 29
   6.1 Biodynamics------------------------------------------------------------------- 30
   6.2 Biokinetics------------------------------------------------------------------- 31
   6.3 Dose finding studies---------------------------------------------------------- 31
   6.4 Clinical efficacy------------------------------------------------------------- 31
   6.5 Clinical safety--------------------------------------------------------------- 32
   6.6 Biovigilance and risk management plan – Class 3 & 4 biologicals only_________ 33

7. Appendices --------------------------------------------------------------------- 34
   Appendix 1 Summaries of compliance with standards----------------------------- 34
   Appendix 2 References------------------------------------------------------------ 34
   Appendix 3 Supplementary dossier information (where applicable)---------------- 34
   Appendix 4 Overseas regulatory information (where applicable)------------------ 35
Introduction

This guidance outlines the information needed in your dossier for us to be able to effectively review your application for a biological therapeutic good.

The kind and form of information that must accompany an application for entry in the ARTG are defined in a legislative instrument under subsections 32DDA (9) and (10) of the Therapeutic Goods Act 1989.

Format of biologicals dossier

Information on the format of your dossier is covered in the following sections:

- **General dossier requirements** which provides:
  - general information for all therapeutic goods dossiers
  - submission details for both electronic and hard copy dossiers

- **Dossier structure** provides an outline of the sections within the dossier for both:
  - TGA dossier structure
  - eCTD dossier structure which provides details about:
    - submitting a dossier in eCTD format
    - including a table to link the TGA dossier structure to the eCTD format.

Content of biologicals dossier

Information on the content you need to include in your dossier is covered in:

- **Technical requirements** you need to address all sections in the dossier structure that apply to your class of biological

  OR

  - justify why a particular section does not apply to your biological.

Guidance on applicable standards

Your dossier needs to demonstrate compliance with applicable standards, including product-specific orders. To assist you when compiling your dossier we suggested you consider our recommendations detailed in:

- **Guidance on TGO 87 - Standards for Labeling**

- **Guidance on TGO 88 - Standards for donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products**

- **guidance on the applicable standards** which indicate where specific clauses are to be documented in your dossier.
International reference and guidance documents

We have provided information on national and international reference and guidance documents to assist you with specific aspects of your application. Such references are not intended to introduce any requirements additional to the applicable standards.

Dossier checklist

The information contained within your dossier:

- **must** demonstrate compliance with all relevant [product-specific and default standards](#) (if applicable)
- is to be formatted according to the headings listed under Dossier structure
- is to address all headings listed in the dossier structure
- is to address and justify if a particular section of the dossier does not apply to your biological
- is to include evidence of manufacturer’s licence or clearance.

We have outlined the type of content we expect you to address in each section to provide us sufficient information to evaluate your submission. We recognise that due to the diversity of biologicals, not all sections outlined may apply to all applications.

If you have questions or need clarification about the dossier requirements please [contact us](#).

We recommend you request a [pre-submission meeting](#) to facilitate the compiling and subsequent submission of your dossier.

Contacting TGA

[contact us](#)
Dossier structure

The dossier can be provided in one of two structures:

- **eCTD dossier structure**
- **TGA biologicals dossier structure**

**eCTD dossier structure**

You may submit your dossier in the electronic Common Technical Document (eCTD) format. The eCTD structure and format requirements are outlined in Electronic submissions. Provide a Table in Section 2.2 that links each section of the TGA biologicals dossier structure with the eCTD structure.

**TGA biologicals dossier structure**

The TGA biologicals dossier structure applies to Class 2, 3 and 4 biologicals. Some sections are class-specific as indicated in the relevant heading, for example:

- **Part 5: Intended use** is for Class 2 biologicals only
- **Part 5: Non-Clinical Development** is for Class 3 & 4 biologicals only
- **Part 6: Clinical development** is for Class 3 & 4 biologicals only

Unless otherwise indicated, the sections listed in the TGA dossier structure apply to all Class 2, 3 and 4 biologicals.

Structure your dossier with the following headings:

1 **INTRODUCTION**
   1.1 Table of contents
   1.2 Submission form
   1.3 Biological lodgement

2 **SCOPE**

3 **RISK MANAGEMENT**

4 **QUALITY AND MANUFACTURING ASPECTS**
   4.1 Biological starting materials
      4.1.1 Donor selection
      4.1.2 Donor blood sampling and testing
      4.1.3 Donor assessment and management
      4.1.4 Collection of starting material
4.2 Manufacturing process
   4.2.1 Manufacturer's details
   4.2.2 Description of manufacturing process and process controls
   4.2.3 Control of material and equipment
   4.2.4 Critical steps and intermediates
   4.2.5 Validation of the manufacturing process

4.3 Characterisation

4.4 Control of final product
   4.4.1 Release specifications
   4.4.2 Analytical procedures
   4.4.3 Validation of analytical methods
   4.4.4 Finished product analysis
   4.4.5 Justification of specifications
   4.4.6 Containers

4.5 Storage and stability
   4.5.1 Stability studies
   4.5.2 Stability data

4.6 Product development

4.7 Labelling and release documentation

4.8 Transportation

5 INTENDED USE – Class 2 only

5 NON-CLINICAL DEVELOPMENT - Class 3 & 4 only
   5.1 Biological dynamics and kinetics
   5.2 Toxicology

6 CLINICAL DEVELOPMENT - Class 3 & 4 only
   6.1 Biodynamics
   6.2 Biokinetics
   6.3 Dose finding studies
   6.4 Clinical Efficacy
   6.5 Clinical Safety
   6.6 Biovigilance and Risk Management Plan

7 APPENDICES

Appendix 1 Summaries of compliance with standards
Appendix 2 References
Appendix 3 Supplementary dossier information
Appendix 4 Overseas regulatory information (if applicable)

Further information regarding the contents of each of these TGA Biologicals Dossier Structure sections is detailed in this document under Technical requirements.
Technical requirements

1. Introduction
In this section, you need to provide general information relating to your submission.

1.1 Table of Contents
Your table of contents is to:

- be formatted with TGA dossier structure headings
- link directly to any reports contained within each section, such as:
  - risk analysis documents
  - standard operating procedures
  - validation reports.
2 Scope

This section is an introduction to your product and is to be written for a general scientific audience. Provide general background information with references and a summary of the complete dossier.

Provide product details, including:

- biological class and product type
- name of the biological and trade name, if applicable
- any individual biologicals to be captured, if applicable.

Provide a general background and dossier summary covering:

- a brief description of the product type and grouped products (when applicable e.g. class 2)
- conceptual aspects and significant elements of the product's design (where applicable e.g. Class 3, 4)
- a brief but current and relevant literature review
- a summary of the manufacturing process
- a summary of the non-clinical development (where applicable, e.g. class 3, 4)
- a summary of the clinical development (where applicable, e.g. Class 3, 4).
3 Risk management

The adoption of a risk management system that applies through all stages of the product's life, from concept and tissue selection/collection to release and intended use, is essential for ensuring optimum product quality and safety. The risk management methodology assists the manufacturer to identify, analyse, evaluate and control the risks in all phases of a products' lifecycle.

ARGB Appendix 11 ‘Risk management’ systematically outlines the approach to be taken to risk management as applicable to biologicals, including a list of references that may be used to guide the development and maintenance of a risk management framework. In addition, the annexes work through clear examples of how risk identification, analysis and management can be performed and documented.

Risk management documentation is to be provided for all Class 2, 3 and 4 biological products to demonstrate that the principles of risk management have been satisfactorily addressed.

Annex 2 of Appendix 11 ‘Risk management’ provides detailed examples on how risk analysis could be applied to a Class 2 biological; and Annex 3 provides an example of how the entire risk analysis and risk management process could be documented.

For Class 3 and 4 biologicals, you must also include:

- a risk analysis to ensure product quality is appropriately controlled, to justify the level of non-clinical and clinical studies on the biological
- a comprehensive post-market biovigilance and risk management plan.
4. Quality and manufacturing aspects

You must address all sections in the dossier structure that apply to your class of biological or justify why a particular section does not apply to your biological.

4.1 Biological starting material

When planning the collection of starting material, it is critical to consider the safety of the recipient. To address the final product’s quality, efficacy and safety in regard to the starting material, the information supplied is to:

- describe in detail the collection process of all biological starting materials
- highlight compliance with relevant standards, when applicable
- outline all donor selection criteria
- include copies of all donor information forms.

**Biological starting material**

You must demonstrate compliance with our Therapeutic Goods (Standard for Human Cell and Tissue Products—Donor Screening Requirement) (TGO 108) Order 2021. Guidance on TGO 108 is to be referred to when preparing your dossier.

Additional information that may be helpful:

- EMEA/CHMP/410869/2006 Guideline on human cell-based medicinal products

4.1.1 Donor selection (Medical and Social history)

Information on your donor selection process must include:

- how you collect the medical and social history of prospective donors
- written criteria for donor selection
- a documented procedure for the interview process
- how any contracting organisations, if used, will be kept up to date with changes to the selection criteria, for example: third party donor selection criteria.
4.1.2 Donor blood sampling & testing

This section requires you to provide details about any donor blood sampling and testing undertaken.

Collection and testing procedures

You must include your written procedures for:

- the collection, storage (archiving) and re-testing of donor blood samples
- donor blood testing
- test kits and methodologies used for evaluating donor blood samples, when performed.

If additional information is needed to interpret infectious disease test results, you must provide documentation. For example, HBV testing algorithms to interpret between:

- NAT positive/serology negative
- NAT negative/serology positive results.

Collection and testing facilities

Infectious disease testing and storage of archived blood samples are manufacturing steps so you must provide:

- a list of all sites that perform testing and storage
  - these are manufacturers and they must have a manufacturing licence
- a copy of all service agreements with any contract laboratories, if used.

4.1.3 Donor evaluation and management

For donor evaluation you need to provide criteria and procedures used for:

- determining donor suitability
- documenting and reviewing donor information and test results
- for donor management you need to cover at least:
  - temporary deferral procedures, for example:
    - a donor suspected to be infected with HIV is to be deferred until an uninfected state can be determined
  - permanent deferral procedures, for example:
    - a donor known to be infected with HIV
- acceptance criteria for donor suitability
- re-admission criteria after a temporary deferral, if applicable, for example:
  - criteria to determine a donor’s suitability after a temporary deferral
  - the diagnostic tests performed post-infection to confirm the absence of an infectious disease
- criteria for acceptance with limited product release, for example:
  - sample collection may be limited to release for autologous use only if a donor tests positive for an infectious disease.
4.1.4 Collection of starting material

Collection procedures for biological starting material is to be well documented and based on the principles of risk management.

Areas to be covered include, but not limited to:

- Physical assessment prior to donation – refer to ARGP Guidance on TGO 88
- Quantity of donation e.g. maximum collection volume or size/mass
- Collection intervals, where applicable
- Collection container such as packs/containers/collection kits (see information box, below)
- List of all critical materials used in collection process, with appropriate quality and safety specifications
- Bioburden sampling, where applicable
- Post-asystole collection times, when appropriate
- Any donor treatment required to facilitate or augment the donation process, for example the treatment with factors to mobilise specific progenitor cells
- Details on labelling are to be included in Section 4.7 of the dossier.

Validation

Include validation of the biological starting material collection process to demonstrate starting material quality.

Storage and stability

Discuss storage and stability of your biological in Section 4.5, even if no manufacturing/processing occurs prior to storage.

Document any transport of the biological starting material from the collection site in Section 4.8; including transport of material to a storage facility.

Collection sites

The need to provide a list of collection sites, and the need for GMP accreditation, will depend on the level of oversight of these sites by the principal manufacturer. For example, where individual collection sites have their own independent collection procedures we would need to ensure that the practices at each collection site are appropriate and comply with applicable standards.

Starting material collection pack/kit

In your dossier provide full details:

- of the pack/kit contents
- of item specifications and its use
- to demonstrate that quality and safety of the biological starting material would not be compromised.

These kits may or may not need to be on the ARTG (as medical devices), depending on whether they are only supplied directly to the manufacturer or also supplied directly to collection sites.
4.2 Manufacturing process

Clearly describe all aspects of the manufacturing process, including:

- compliance with relevant standards, when applicable
- transportation from collection of the starting material through to the final product release

Provide sufficient information to show:

- your manufacturing process has been designed to ensure product consistency
- a risk management approach was used to establish in-process controls and specifications.

You need to provide information on all manufacturers of your biological. This includes:

- all testing facilities you use for donor infectious disease testing
- all microbiology testing facilities
- sterilisation and/or irradiation facilities
- any packaging facilities.

You must have a pending, or approved, manufacturing licence or clearance for all manufacturers before submitting an application.

4.2.1 Manufacturer’s details

In this section, you need to provide details on all of your manufacturers and manufacturing sites. A tabulated format is preferred containing the following information:

- name
- address
- manufacturing process – detailed steps
- TGA GMP licence or certification information, such as:
  - a current GMP licence
  - a current GMP certificate or clearance
  - evidence of an application for a licence to manufacture therapeutic goods in Australia
  - evidence of an application for a GMP certificate for an overseas manufacturer submitted to the Manufacturing Quality Branch.

**Collection sites**

List manufacturers involved solely in collection of biological starting material in Section 4.1.4.

**Disease testing**

List manufacturers involved solely in infectious disease testing relating to donor evaluation in Section 4.1.2.
4.2.2 Description of manufacturing process and process controls

Include:

- a description of the entire manufacturing process:
  - from completion of the collection of the biological starting material through to final product release
  - for example, transport of starting material to the manufacturer, cryopreservation, labelling and storage

- an annotated flow diagram indicating both:
  - the critical steps
  - in-process control points

- detailed microbial control steps

- a documented policy for product reprocessing, if applicable.

**Class 2**

- For all **Class 2 biologicals** include a statement that the manufacturing process comprises processes considered ‘minimal manipulation’.

4.2.3 Control of critical material

In this section, you need to provide a list of all **critical materials**, including any excipients, vectors and medical devices used in the manufacturing process.

Your **critical materials list** should include, but not be limited to:

- name of material
- source (company) of material
- the role of the material in the manufacturing process
- quantity used in the manufacturing process (when applicable)
- if material is registered on ARTG or not
- if the material complies with a defined Standard (e.g. Pharmacopoeial monograph) or in-house specifications.

If the critical material is not on the Register, or a default standard does not apply, you must provide information to:

- **characterise** the critical material
- **demonstrate control** of the quality and safety of the material.

The level of control of each material is to reflect both:

- its use
- potential risk to the product.
More detail on minimal information required on critical materials, including solutions, antimicrobial agents, or material containing any components of human or animal origin, is discussed in Guidance to TGO 88.

**Submitting in-confidence data**

If you have data that is in-confidence to the material manufacturer, you may submit it directly to us under the provisions in the *Therapeutic Goods Regulations 1990*, Regulation 16 GF for data (e.g. about a critical material).

### Additional controls for Class 3 and Class 4 biologicals

Manufacture of Class 3 and Class 4 biologicals may require the following additional controls, if there is a likelihood of an impact on the quality, safety or efficacy of the finished biological:

- **Cell banking** is to be described in accordance with the guidelines in:
  - [ICH O5D: Derivation and characterisation of cell substrates used for production of biotechnological/biological products](https://www.ich.org/ich-guidelines)

- When **bovine serum** is used, follow the recommendations in:
  
    Note that the use of irradiated sera and/or synthetic alternatives is encouraged.

- Describe any Class 4 biologicals that use **vectors or other gene transfer procedures** in accordance with:

### 4.2.4 Critical steps and intermediates

In this section, you need to provide a full description, including acceptance criteria, of all:

- critical control points (in-process controls)
- key elements, as informed by risk analysis.

**Quarantine steps**

Discuss quarantine measures for:

- biological starting material and donor blood/plasma samples during donor testing
- autologous material found to be infectious disease positive.

**Microbial control measures**

Discuss microbial control measures, including but not limited to:

- bioburden sampling points (pre- and post-processing sampling)
- appropriate bioburden specifications at each stage
• bioburden reduction strategies, if applicable
• where appropriate, provide a list of organisms tested, including ‘allowed’ organisms (if positive growth is identified)
• aseptic processing, if applicable.

### 4.2.5 Validation of the manufacturing process

In this section, you must present validation data for each step in the manufacturing process.

Validation of microbiological methods is described in the default pharmacopoeial standards (BP, Ph.Eur, USP) and in the following ISO standards:


**Class 3 and 4 biologicals:**

Additional requirements that may apply to your biologicals are:

- where terminal sterilisation is not an option, aseptic process is required and **must** be validated
- viral removal or reduction steps **must** be validated, if performed
- in case of limited sample availability, and where justified, more extensive validation is to be performed using samples with comparable characteristics.

**Validation methodologies**

If further information is required, guidance on possible methodologies that could be used is in:

- ICH Q2R1: Validation of Analytical Procedures: Text and Methodology

### 4.3 Characterisation

**Class 2 biologicals**

In this section, the information provided is to be a broad characterisation of the biological during product development. You need to:

- identify critical quality attributes
- provide crucial reference points for determining the effect of a variation to the manufacturing process.

Where characterisation studies are performed on the product at any stage of the manufacturing process, **beyond** those routinely performed as part of in-process testing or as release criteria, they are also to be documented here.
Generally for Class 2 biologicals such additional studies would not be performed. An example of where such studies may be performed could be the characterisation by microarray of the gene expression profile of cultured cells at various stages of expansion. In-process controls and specifications would not capture all the details. The additional studies provide confidence to both the manufacturer and regulator that the process is satisfactorily controlled. In addition, such studies can be crucial if changes are introduced to the cell culture process.

**Class 3 & 4 biologicals**

In this section, the information provided is to be an extensive characterisation of the biological, including:

- biological and non-biological components,
- a profile of any potential toxicities, and
- the finished product.

This characterisation is to be above and beyond the scope of the standard manufacturing in-process controls and release criteria.

**Requirement for characterisation studies**

Characterisation studies are to:

- identify critical quality attributes and,
- provide crucial reference points for determining the effect of a variation to the manufacturing process so product comparability can be fully and accurately assessed.

An example of where such studies may be performed could be the characterisation by microarray of the gene expression profile of cultured cells at various stages of expansion. In-process controls and specifications would not capture all the details. The additional studies provide confidence to both the manufacturer and regulator that the process is satisfactorily controlled. In addition, such studies can be crucial if changes are introduced to the cell culture process.

**4.4 Control of finished product**

The specifications of the finished product must be fully determined and controlled if the quality is to be ensured. A risk analysis and management strategy is used to inform the final product specifications, in conjunction with characterisation studies and relevant standards.

**4.4.1 Release specifications**

Your finished product release specifications are to include, but not be limited to:

- Key parameters identified as crucial to product quality, purity and effectiveness (e.g. cell number/viability)
- Specifications identified in default standards and/or Orders
- Endotoxin limits
- Completed infectious disease screening
- Microbial control and/or Sterility
- Processing times met, where applicable
- Examination and evaluation of cells or tissue prior to release, where appropriate.
4.4.2 Analytical procedures

You need to provide a list and attach copies of:

- all analytical procedures
- all reference standards
  - primary reference material is to be established for all critical assays used in the testing of finished product
  - all materials.

Where applicable, also include the following information on your reference material:

- calibration of reference material against a national or international standard, if available
- where appropriate, for all reference material provide:
  - a description of the preparation
  - documentation of its characterisation
  - details of its storage conditions.

4.4.3 Validation of analytical methods

In this section, you must present validation data for all analytical procedures used. Validation of microbiological methods is described in the default pharmacopoeial standards (BP, Ph.Eur, USP) and in the following ISO standards:


Class 3 and 4 biologicals

Additional requirements that may apply to your biological are:

- where terminal sterilisation is not an option, aseptic process is required and must be validated
- viral removal or reduction steps must be validated, if performed
- in case of limited sample availability, and where justified, more extensive validation is to be performed using samples with comparable characteristics.

**Validation methodologies**

If further information is required, guidance on possible methodologies that could be used is in:

- ICH Q2R1: Validation of Analytical Procedures: Text and Methodology
4.4.4 Finished product analysis
You must demonstrate that your manufacturing process is able to consistently produce final product within the stated specifications.

You need to state and justify the number of manufacturing runs needed to be analysed to demonstrate process consistency.

4.4.5 Justification of specifications
Justify all of your release specifications against all of the appropriate:

- relevant standards
- published literature
- process validation.

4.4.6 Containers
You must demonstrate the suitability of the container/s used for the final product, including:

- information and validation of container type
- container and closure material
- compliance to relevant standards, where applicable.

4.5 Storage and stability
Biological materials are particularly sensitive to adverse conditions. As such, an investigation of the stability of the final product is to be performed. This is used to set storage conditions and justify the proposed shelf-life.

Class 2 biologicals

This section only applies to Class 2 biologicals.

Class 3 & Class 4 biologicals must include stability studies as outlined below.

The storage conditions and shelf-life of the biological is to:

- comply with the product-specific standard
  OR
- be justified based on either submitted data or literature.

If stability studies have been performed, provide a summary of the studies and conclusions.

In case of limited sample availability, and where justified, more extensive stability studies could be performed with samples of comparable characteristics.
Class 3 & 4 biologicals

This section only applies to Class 3 & Class 4 biologicals which must include stability information as outlined below.

4.5.1 Stability studies
You must include a summary of the stability studies and conclusions. This is to be tabulated, showing the time since the commencement of the study against the specific parameters.

State all post-approval commitments, e.g. the reporting to the TGA of any out-of-specification observations in long-term stability studies that are ongoing post-approval.

In case of limited sample availability, and where justified, more extensive stability studies could be performed with samples of comparable characteristics.

4.5.2 Stability data
Provide result tables for all stability studies here.

4.6 Product development
It is expected that manufacturing processes will change from the design phase to the current practice, for example, due to improved technology or increased scale of production.

In this section, you are required to document major studies or validations performed before a significant change, was introduced to the manufacturing process. This section does not require documentation of all changes.

A significant change is one that has the potential to alter the function of the final product. When this occurs, you need to demonstrate whether earlier studies are still applicable. The level of documentation is to include, but not be limited to, discussing or demonstrating product comparability.

4.7 Labelling and release documentation
In this section, you need to demonstrate traceability of the biological material throughout its life cycle from initial donor selection to administration of the finished product. The information provided in this section:

- must demonstrate compliance with TGO 87 – General requirements for the Labelling of Biologicals
- must include examples of all unfilled labels, and any accompanying documentation
- must demonstrate traceability of biological material from initial donor and throughout the manufacturing process
- is to include labelling examples to scale and in colour, where applicable
- is to include copies of documentation outlined in TGO 87. We also encourage supply of release documentation detailing additional product information, e.g. results of release testing.
In the following situations, additional information is required:

- where bioburden testing identified growth of ‘allowed’/acceptable organisms, the release labels and accompanying documents are to contain this information, where allowed in a specific TGO
- where infectious disease testing is positive, the release labels are to contain this information, and will only be acceptable if the label states ‘for autologous use only’
- when required by a product specific standard, evidence of microbial contamination of a released product must be supplied to persons detailed in the product specific standard.

**Outer container labels** and **transport labels** are to be detailed under Section 4.8 Transportation.

---

**Traceability and labelling**

Traceability of biological material is a critical component of product labelling and documentation. This is achieved by a single rational labelling system that can be used by everyone involved in the collection, manufacturing and administration of the biological. The final product label and accompanying release documentation is critical to informing the end user and recipient of the quality, safety and efficacy of the biological.

---

**4.8 Transportation**

In this section, you need to provide information on all transportation of the biological during any stage of the manufacturing process, from the collection of the starting material to the release of the final product.

Packaging, labelling and temperature for transportation are to:

- comply with **product-specific standards**
- comply with local laws and regulations
- be fully validated.

You must provide information on transportation of the biological during all stage of its manufacturer, including:

- transportation of the starting material from the collection site to the manufacturing site
- transportation between manufacturing sites
- transportation and packing procedures, including:
  - labelling
  - full validation data with respect to temperature and integrity.
5. Intended use – Class 2 biologicals only

You must justify the efficacy of a Class 2 biological based on the product’s ‘intended use’ by including a supporting statement in this section of your dossier. Where a Class 2 dossier contains a number of products, provide evidence to support all products.

How intended use differs from indication

‘Intended use’ reflects:

- the broad clinical use of the product
- is not required to be supported by product specific clinical data.

This differs to the pharmaceutical concept of 'indication' which is usually:

- related to a specific product and disease/patient group
- must be supported by product specific clinical data.

Justifying efficacy in your supporting statement

Provide a brief summary of evidence to support the intended use, by including:

- evidence drawn from the scientific literature, include appropriate:
  - reviews or reference to standard texts
  - clinical usage guidelines
- how the evidence is relevant to the biological product and route of administration
- may include (or reference) clinical data, but this is not required.

Completing the biologicals application form

When completing the biologicals application form, you are asked to select an intended use from a drop down menu. If a suitable intended use is not available contact us, as additional intended use ‘phrases’ can be added, if appropriate.

5.1 Risk Management Plan – upon request only for Class 2 biologicals

If we identify any safety concerns, which require additional biovigilance or risk minimisation, we may request that you submit a risk management plan (RMP) with your application for inclusion on the ARTG.

If you are requested to submit a RMP, information is available in Risk management plans for medicines and biologicals.
5. Non-clinical development – Class 3 & 4 biologicals only

Purpose of non-clinical development

Prior to conducting clinical trials, it is essential to understand the biological dynamics/kinetics and toxicology of a biological by providing information from both:

- *in vitro* testing
- animal studies.

These studies provide detailed fundamental biological, pharmacological and toxicological information concerning the biological for human-based clinical trials.

The information provided for the non-clinical studies needs to:

- demonstrate proof-of-principle
- define the biological dynamics/kinetics
- define the toxicological effects predictive of the human response both:
  - prior to initiation of clinical trials
  - throughout clinical development and application.

Required information

It is expected that information on the following aspects of the studies be included:

- dose-response relationship
- selection of safe doses for clinical trials
- the route of administration and the application schedule
- duration of exposure
- duration of the follow-up time to detect adverse reactions
- identified target organs for toxicity and
- monitor parameters in patients receiving these therapies.

Recommended tests

If a recommended test is not performed, sound and relevant scientific justification for not conducting the test is required e.g., the test has been performed for another product of the same composition, manufacture, indication and administration from the manufacturer.

Supporting publications

Relevant published studies could be sources of information to support the application. Such studies:

- are often not designed to answer pharmacological or toxicological questions
- usually do not contain sufficient information for an independent review (e.g., raw data)
- test products that are not immediately comparable to the finished biological.

Adequate pharmacological/toxicological endpoints may not have been incorporated into the studies, which mean the results are not readily applicable to the biological. Nevertheless, the information may compliment unpublished studies designed specifically for the biological to support the application.
For further guidance on non-clinical data requirements please refer to the relevant EU guidelines, for example:

- **EMEA/CHMP/410869/2006** Guideline on human cell-based medicinal products
- **3AB6a**: Gene Therapy product quality aspects in the production of vectors and genetically modified somatic cells

For further guidance on quality and manufacturing aspects:

- **EMA/CAT/571134/2009**: EMEA Reflection paper on Stem cell based product 2000
- **EMA/319294/2010**: Summary report on the EMA workshop on stem cell-based therapies
- **EMA/CAT/571134/2009**: Reflection paper on stem cell-based medicinal products
- **Multidisciplinary: Cell therapy and tissue engineering guidelines**
- **EMA/CAT/486831/2008/corr**: Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products

### 5.1 Biological dynamics and kinetics

Once your non-clinical studies have demonstrated proof of principle, further animal model studies are required. It is necessary to examine potentially undesirable physiological effects of the biological including their bioactive products.

#### Required information

In this section, include information on:

- kinetics, migration and persistence studies to demonstrate:
  - tissue distribution
  - viability
  - trafficking
  - growth and phenotype
  - any alteration of phenotype due to factors in the new environment

- animal studies (with appropriate ethics approval) to evaluate any clinical concerns regarding undesirable physiological effects and possible adverse reactions, such as if cells migrate within the host.

- cell-based products that produce **systemically active molecules**, including information on:
  - the distribution
  - duration
  - amount of expression of these molecules
  - the survival and the functional stability of the cells at target sites
• possible interactions of the applied biological with surrounding cells and tissues
• interactions studies examining the interaction of the applied biological or its surrounding tissue with the non-cellular structural components and other bioactive molecules
• Proof of concept/principle studies \textit{in vitro} and/or \textit{in vivo}
• Safety pharmacology studies are considered on a case-by-case basis, depending on the characteristics of the product. e.g. cells may secrete pharmacologically active substance.

Conventional absorption, distribution, metabolism and excretion studies are usually not relevant for biologicals.

5.2 Toxicology

The need for toxicological studies varies depending on the nature of the product. The application and appropriateness of conventional toxicological studies (single and/or repeat dose studies) must be assessed for each biological product.

When conventional study designs are considered not appropriate or feasible, provide scientific justification for the models used, or the omission of studies.

Toxicity may occur, for example, due to unknown cellular alterations developed during the manufacturing process such as altered excretion patterns and \textit{in vivo} behaviour due to differentiation of the cells.

Required information

In general, non-clinical studies are to include the following toxicology information:

• Single and repeated dose toxicity studies
• Local tolerance studies
• Additional toxicity studies
  – Immunogenicity/auto-immunity studies
  – Tumorigenesis /carcinogenesis: case-by-case basis
  – Genotoxicity if there is a potential for the product to interact with genetic materials
  – Reproductive/developmental – case-by-case basis.

The need for genotoxicity, developmental and reproductive toxicity studies are to be considered on a case-by-case basis.

Other potential factors that may induce toxicity, to be addressed, include the presence of components that are:

• used in the manufacturing process
• part of a structural component,
• part of proliferation of the applied cells in an unwanted quantity or in an unwanted location.
6. Clinical development – Class 3 & 4 biologicals only

To determine the extent of data required for marketing approval, a risk-based approach is used, based on:

- risks inherent to the product in question
- risks associated with the product’s quality, safety and efficacy.

This information is to be clearly distinguished from risk management.

EU guidance on a risk-based approach:


This EU guidance includes examples of risk factors for cell-based and gene therapy products, which you may find useful in identifying and developing:

- discussion regarding justification of the extent of quality
- non-clinical data
- clinical data.

Background

Human-derived cell and tissue therapies present novel challenges in clinical development programs. Such products may be:

- heterogeneous in origin and type of cells
- autologous or allogeneic
- self-renewing stem cells
- committed progenitor cells
- terminally differentiated cells which have a specific physiological function
- expanded ex-vivo
- induced to differentiate along a particular pathway
- genetically modified
- used alone
- associated with biomolecules or other chemical substances
- combined with structural materials.

Human-derived cell or tissue therapy products have specific biological characteristics. As such, approaches to Phase I to III clinical trials may require alternative approaches to those used for other medicinal products.
Required information

Requirements for clinical evaluation are intended as guidance for human-derived cell and tissue products applying for inclusion on the ARTG, but these principles are to also be considered for products entering into clinical trials.

The requirements outlined in this section are based on EU guidelines:

- **EMEA/CHMP/410869/2006**: Guideline on human cell-based medicinal products
- **EMEA/CHMP/149995/2008**: Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products
- **CHMP/ICH/2887/99 Rev 1 Efficacy**: Common Technical Document for the Registration of Pharmaceuticals for Human Use – Clinical Overview and Clinical Summary of Module 2 and Module 5: Clinical Study Reports

Clinical development

Integral parts of clinical development studies that are to be fully described in this section, include:

- standardisation and optimisation of the therapeutic procedure as a whole
- the method of administration
- required concomitant medication such as immunosuppressive regimens.

We recognise that the diversity of human and animal cell-based products can lead to:

- very different levels of risk to patients, medical personnel or the general population
- varied development plans and evaluation requirements based on a multifactorial risk-based approach.

We strongly recommend early consultation with us regarding uncertainties in the rationale of clinical development programs, including confirmatory studies, when marketing authorisation may be sought.

Additional data

Depending on the risk of the product, some sections of the application dossier may be either:

- complemented with additional data where necessary
  
  OR
  
- limited when **appropriately justified** on the basis of risk.

Proof or principle

If appropriate clinically meaningful endpoints are provided for safety and efficacy evaluation, it may be useful when demonstrating 'proof of principle', to provide:

- relevant non-clinical studies
- previous clinical experience of the treated pathology
- initial clinical studies.
Factors that impact final use of product
Address any requirements identified during clinical development programs that impact the final use of the product. For example, biological effects that are highly dependent on the in vivo environment and may be:

- influenced by the replacement process; or,
- immune reactions of the patient or from the product.

Administration routes
Provide information on administration requirements of the product such as:

- administration via specific surgical procedures
- being combined with other treatments to obtain the intended therapeutic effect.

6.1 Biodynamics
Include in this section:

- the main effects of the biological, even where the mechanism of action is not well understood
- details of functional tests performed when the purpose is to either:
  - correct deficient functions
  - destroy cells or tissues
- details of any structural or histological assays, if the intended use is to restore or replace cells or tissues with an expected lifelong functionality; these might include, but are not limited to:
  - structural or histological assays, which may be potential biodynamic markers. These might include, but are not limited to, microscopic techniques
  - histological techniques
  - imaging techniques
  - enzymatic activities
  - expression of cellular antigens
  - proteomics and functional genomics analysis
- assessment methods for any non-cellular components combined with a human cell-based product, such as:
  - compatibility
  - degradation rate
  - functionality.
6.2 Biokinetics

Conventional absorption, distribution, metabolism and elimination (ADME) studies are usually not relevant for biologicals.

Possible methodologies for assessing biokinetics of human cell-based products during the period of intended utility of the product are to be addressed to monitor:

- viability
- proliferation/differentiation
- body distribution/migration and functionality during the period of intended utility of the product.

If multiple administrations are necessary, address the schedule in terms of the expected in vivo life span of the human cell-based product.

6.3 Dose finding studies

Dose selection is to be:

- based on findings from the quality and non-clinical development of the product
- be linked with the potency of the product.

Individualised dosage

Where dosage is individualised for the intended recipient the dose to be tested in the confirmatory trial is to be supported by the evidence provided in Phase I/II studies.

Minimal effective dosage

Phase I/II studies are to be designed to identify either the:

- Minimal Effective Dose, which is the lowest dose required to obtain the intended effect
- Optimal Dose Range, which is the largest dose range required to obtain the intended effect, based on clinical results for efficacy and tolerability.

Safe maximal dose

If possible, also investigate the safe maximal dose. This is the maximal dose which could be administered on the basis of clinical safety studies without unacceptable adverse effects, taking into account, if necessary, the possibility of repeated administration schedules.

6.4 Clinical efficacy

Clinical efficacy studies need to demonstrate efficacy in the target patient population, whilst ensuring:

- clinically meaningful endpoints
- demonstration of an appropriate dose-schedule that results in the optimal therapeutic effect
- evaluation of the duration of therapeutic effect of the administered product
- risk-benefit assessment, taking into account the existing therapeutic alternatives for the target population.
Confirmatory studies

Confirmatory studies are to be in accordance with existing general and specific guidelines for the condition being evaluated.

Deviations from such guidelines must be justified – for example, even if the nature and mechanism of action for a human cell-based product is entirely novel, this does not necessarily mean that therapeutic benefit should be measured by different end-points from those recommended in current disease-specific guidelines (e.g. medicine vs. cell implants for Parkinson's disease).

Use of endpoints

The use of previously validated or generally accepted surrogate endpoints is possible provided that a correlation between clinically meaningful endpoints and efficacy can be established and justified.

- In some cases, the desired clinical endpoint, e.g. prevention of arthropathy, can only be observed after prolonged follow up, and marketing authorisation may be based on surrogate markers.
- If efficacy is dependent on long-term persistence of the product, a long-term follow-up plan for patients must be provided.

6.5 Clinical safety

The safety database provided is to be capable of detecting common adverse effects.

The size of the database may be informed by previous clinical experience with similar products.

Safety issues

Address all safety issues from the preclinical development program, especially:

- in the absence of an animal model of the treated disease
  OR
- in the presence of physiological differences limiting the predictive power of an homologous animal model.

Procedural risks

Provide sufficient information on the risk of the therapeutic procedure as a whole to justify both the:

- clinical studies
  AND
- choice of the target patient population.
Biological processes

Particular attention must be paid to biological processes which occur during the development and post-marketing phases of human cell-based products, including but not limited to:

- immune response
- infections
- malignant transformation
- concomitant treatment.

Clinical safety studies on repeated administrations are to be performed as required by a risk analysis.

For products with expected long-term viability, plans for patient follow-up are to be provided to ensure surveillance of long-term efficacy and safety issues related to the product.

6.6 Biovigilance and risk management plan – Class 3 & 4 biologicals only

As a sponsor of a biological, you need to be aware of your responsibilities, refer to:

- Biovigilance responsibilities of sponsors of biologicals

All Class 3 & 4 biologicals must provide a Risk Management Plan (RMP) describing routine biovigilance and traceability of the biological. Base your RMP on the considerations outlined in:

- EMEA/CHMP/149995/2008: Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products

Traceability

Traceability in the donor-product-recipient axis, or in the product-recipient axis for autologous products, is required in all circumstances.

Long term studies

Human-derived cell and tissue products may need special long-term studies to monitor specific safety issues, such as:

- infections
- immunogenicity/immunosuppression
- malignant transformation
- loss of efficacy
- in vivo durability of any associated medical device/biomaterial component, which must be addressed in the RMP.

Bio-epidemiological studies

Specific requirements linked to the biological characteristics of the cell-based product may require special bio-epidemiological studies.
7. Appendices

Provide appendices as outlined in this section with your dossier.

Appendix 1 Summaries of compliance with standards

You are required to include in this Appendix, all relevant ‘Location of requirements in dossier’ tables, provided in:

- Guidance for TGO 87

AND

- Guidance for the relevant product-specific TGOs.

You must complete the column in these tables entitled ‘Summary of how requirement is met’, briefly describing the information in the dossier that addresses each individual clause.

Appendix 2 References

You must provide copies of all papers used as:

- supporting evidence
- to justify any specifications.

All other references used in your dossier need only to be listed in this appendix.

Appendix 3 Supplementary dossier information (where applicable)

Related TGA applications

If your application depends upon the outcome of, or relate to, any other application currently under evaluation by TGA, please provide submission number(s) and/or TGA numbers in this section.

In-confidence data

If your application makes reference to ‘in confidence’ data, submitted by manufacturers directly to the TGA for evaluation, you must provide written permission from the owner of the confidential information allowing the TGA to access that information on behalf of the applicant; such as:

- information on the manufacture of a critical material
- Drug Master File (DMF)
- Plasma Master File (PMF)
- Biological Master File (BMF)
- European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP).
Pre-submission meetings
If you attended any pre-submission meetings, please detail:

• agenda
• conclusions
• contact person
• attach any pertinent emails, minutes from meetings, letters etc.

Other relevant information
If there is any other pertinent information that would assist us with the evaluation of the dossier, for example planned changes to the contact person or planned changes to company details, include it in this section.

Appendix 4 Overseas regulatory information (where applicable)

Commercial history
Please detail the commercial history, including:

• date of first clinical application of the product
• marketing in each country other than Australia.

Overseas regulatory status
Please detail the regulatory status in each country other than Australia, including:

• approvals
• rejections
• severe adverse reactions linked to the product and recalls.
## Version history

<table>
<thead>
<tr>
<th>Version</th>
<th>Description of change</th>
<th>Author</th>
<th>Effective date</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1.0</td>
<td>Original publication incorporating information previously published on the TGA website</td>
<td>Biological Science Section Regulatory Guidance Team</td>
<td>July 2018</td>
</tr>
<tr>
<td>V1.1</td>
<td>Original publication incorporating information previously published on the TGA website</td>
<td>Biological Science Section Regulatory Guidance Team</td>
<td>November 2021</td>
</tr>
</tbody>
</table>
Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication # D18-10597208