Australian Government
Department of Health
Therapeutic Goods Administration

Australian Regulatory Guidelines for Biologicals

Appendix 3 – Guidelines on Class 4 Biological dossier requirements

Version 1.1, March 2018

TGA Health Safety Regulation

Contents

Introduction

This part of the guidance document outlines the format and contents of a dossier that is to be submitted in support of an application for a biological therapeutic good.

The general format of the submitted dossier is outlined in the class-specific guidelines under 'General requirements'. It is suggested that the dossier be divided into clearly identified sections covering the scope of the application, risk management, quality and manufacturing aspects. In other parts of the guidance covering the labelling, infectious disease and product-specific orders, tables are provided to guide the Sponsor to where individual clauses should be discussed within the dossier.

Under each heading information is provided to assist the Sponsor as to the content that should be included. The suggested content identifies key aspects that should generally apply to any biological application, but it is recognised that due to the diversity of potential biologicals, all of the sections/points may not apply to a specific application. Where possible, references are made to national and international reference and guidance documents that can be used to assist the Sponsor with specific aspects of the application. Importantly, these statements are not intended to introduce any additional requirements above the applicable Standards, rather they articulate mechanisms for compliance.

It should be noted that in the guidelines the headings and contents throughout Parts 1-4 are broadly applicable across Classes 2, 3 and 4, as are the non-clinical and clinical development parts (Parts 5-6) for Class 3 & 4 biologicals.

If there are any questions, or if clarification is required in relation to this guidance on the dossier requirements for a biological, please contact the TGA, Biological Sciences Section either by phone, e-mail or in writing, as detailed on our website. We recommend meeting directly with the TGA in a pre-submission process to facilitate the compiling and subsequent submission of the dossier.

The information contained within the dossier must demonstrate compliance with all relevant product-specific and default standards (if applicable). It should also more broadly address all headings listed in the dossier structure. If a particular section/point of the dossier does not apply to the biological in question, this should be stated and a justification given.

To assist applicants to systematically address the requirements outlined in TGO 87 (General requirements for the labelling of biologicals) and product-specific orders, tables are provided within their guidance documents that indicate where individual clauses should be documented in the main dossier. It is suggested that the recommendations for donor selection, testing and minimising infectious disease detailed in ARGB Appendix 4 ARGB Appendix 4 are considered when completing this dossier. Please contact the TGA if any clarification is required.

The technical requirements stated for the dossier should be strictly adhered to.

General requirements

Text Requirements

The dossier must be written in English.

Where supporting material is not originally in English, a copy in the original language and a full translation must be submitted, the accuracy of which is the responsibility of the sponsor.

Font sizes for text and tables must be of a style that are large enough to be easily legible, even after photocopying or when provided electronically.

Generally, a font size of 10 points is considered acceptable in tables, but fonts smaller than 12 points should be avoided whenever possible.

Times New Roman, 12 point font is recommended for narrative text.

Times New Roman, 10 point font is recommended for footnotes.

Page layout

The dossier MUST be formatted according to the headings listed under Dossier Structure.

Sequential page number, month/year and manufacturer name should be included as a footer to every page in the dossier. Sections can be paginated individually.

Appendices should be set out in a legible format, footnoted with appendix number, continuation of sequential page numbering (following on from the main dossier page numbers), month/year and manufacturer name.

Text, tables and figures must be prepared using margins that allow the documents to be printed on A4 paper.

The left-hand margin must be sufficiently large that information is not obscured through binding.

A table of contents, including any attachments, should be provided.

Dossier submission

A table of contents, including indexing, must be included. The dossier MUST be formatted according to the headings listed under Dossier Structure.

Electronic versions of the dossiers should be sent to:

Therapeutic Goods Administration
Department of Health
PO BOX 100
MDP122
WODEN ACT 2606

or delivered by courier to:

Therapeutic Goods Administration
136 Narrabundah Lane
SYMONSTON ACT 2609

You can send one electronic copy of your dossier using one set of the following media:

- single-sided CD-R or DVD-R (single or dual layer)
- USB flash drive
- USB external hard drive.

Any scanned components should be inserted into the Microsoft Word version as JPEG files, or provided in PDF format.

- Sponsors must provide the electronic submission dossier on the smallest number of media units possible, taking into consideration the size of the submission. If more than one unit is needed, avoid spanning the content of a part or a Section of the dossier over two units.
- PDF files produced from an electronic source document are highly preferred over PDF files produced from scanned paper, since those 'electronic' PDF files provide the maximum functionality to the reviewers in terms of search and print capabilities, and copy and paste functionality.

Dossier structure

The dossier can be provided in one of two structures:

TGA Biologicals Dossier Structure

The following headings form the structure by which the dossier should be compiled:

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

4.2.4 Critical steps and intermediates

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

eCTD Dossier Structure

The dossier may be submitted in the electronic Common Technical Document (eCTD) format.

Full details of the eCTD structure and format can be found using the Electronic submissions TGA webpage.

If submitted in eCTD format, a Table should be included in Section 2.2 to provide links between each section of the TGA Biologicals Dossier structure and where this information is included in the eCTD structure.

Technical requirements

1. Introduction

The section contains general information relating to the submission.

1.1 Table of contents (TOC)

The TOC must be formatted according to the headings listed under Dossier Structure and contain sufficient additional information to allow quick location of any reports contained within the sections; such as risk analysis documents, standard operating procedures, and validation reports.

1.2 Submission form

At the completion of biological application, a copy of the eBS 'Submission Document for a Biological Application' must be included in the dossier.

1.3 Biological lodgement

At completion of biological application through eBS, a copy of the full 'Biological Lodgement' must be included in the dossier.

2. Scope

The scope of this application should detail the Class 4 Biological product including name, trade name if applicable.

This section is an introduction to the product, including general background information and a summary of the complete dossier. This should be written for a general scientific audience. The introduction should address:

- A brief description of the product that also addresses conceptual aspects and significant elements of the product's design. References should be listed.
- A brief but current and relevant literature review
- A summary of the manufacturing process
- A summary of the non-clinical development
- A summary of the clinical development

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 should assist 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 that should 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 should be provided for all class 4 biological products to demonstrate that the principles of risk management have been satisfactorily addressed. Importantly, risk analysis should be performed to ensure product quality is appropriately

controlled, to justify the level of non-clinical and clinical studies on the biological, and a comprehensive post-market biovigilance and risk management plan must be included.

Annex 2 of Appendix 11 'Risk management' provides detailed examples on how risk analysis process could be applied to a class 3/4 biological; and Annex 3 provides an example of how the entire risk analysis and risk management process could be documented.

4. Quality and manufacturing aspects

4.1. Biological starting material

The information supplied should clearly describe all aspects of the collection of the biological starting materials, highlighting compliance with relevant standards when applicable and provide details of any additional criteria that are essential to the safety, quality and efficacy for the finished product. Consideration of final product quality, efficacy and safety, and hence recipient safety, is of utmost importance when planning and carrying out the collection of the starting material. Copies of all associated documents, such as donor selection criteria and donor information forms should be supplied.

Further guidance on the collection of biological starting materials can be obtained from the EMEA document "Guideline on human cell-based medicinal products"

4.1.1 Donor selection (Medical and Social history)

There should be written criteria for donor selection, and a documented procedure for the interview process.

These documents must capture the medical and social history of prospective donors.

If a Third party donor selection criteria is utilised, it should be clearly stated how the contracting organisation will be kept up to date with changes to the selection criteria.

4.1.2 Donor blood sampling & testing

There must be written procedures for the collection, storage (archiving) and re-testing of donor blood samples.

Procedures relating to donor blood testing must be documented.

The test kits/methodologies used in the evaluation of donor samples must be recorded in written procedures and/or in the service agreement with contracted testing laboratory.

Where required, any additional information necessary for interpretation of individual infectious disease testing results, must be documented. For example, HBV testing algorithms to interpret e.g. NAT positive/serology negative or NAT negative/serology positive results.

A list of all sites that perform infectious disease testing and storage of archived blood samples, must be provided as these are considered manufacturing steps. If a contract laboratory is used a copy of the service agreement should be provided. Renewal of these contracts will be assessed as part of audits, but entering a contract with a new provider represents a variation to the manufacturing process and TGA must be notified.

4.1.3 Donor evaluation and management

The donor selection documentation and testing results must be reviewed and evaluated to determine suitability of the donor.

The criteria and procedure for determination of donor suitability and for donor management should be documented.

For donor management, areas to be covered should include, but not be limited to:

- temporary deferral, e.g. a donor suspected to be infected with HIV should be deferred until an uninfected state can be determined.
- permanent deferral, e.g. a donor known to be infected with HIV.
- acceptance criteria

- re-admission criteria post-deferral, if applicable e.g. the timeframe following a temporary deferral beyond which a donation would be accepted, or specific blood tests that would be carried out to confirm the absence of an infectious disease agent post-infection
- criteria for acceptance with limited product release, e.g. collection for autologous release only when a donor tests positive for an infectious disease agent.

4.1.4 Collection of Starting Material

The procedures for collection of the biological starting material from the donor should be provided in the dossier, and be based on the principles of risk management.

Areas to be covered should include, but not be limited to:

- Physical assessment prior to donation – refer to ARGB Appendix 4
- Quantity of donation e.g. maximum collection volume or size/mass
- Collection intervals, where applicable
- 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 should be included in Section 4.7 of the dossier.

A list of collection sites, including addresses, should be provided.

Validation of the biological starting material collection process should be included, to demonstrate starting material quality.

If no manufacturer/processing occurs prior to storage, the storage and stability of the biological should still be discussed in Section 4.5 of the dossier.

Any transport of the biological starting material from the collection site should be documented in Section 4.8 of the dossier; including transport of material to a storage facility.

Where the starting material collection pack/kit assembled by the manufacturer is only for use in relation to that manufacturer, whether in a surgical or mortuary environment, and are not supplied outside the manufacturer's governance, they are not required to be included on the ARTG. The manufacturer's obligation, however, in respect of the cGMP means that product(s) used in collection and manufacture of the therapeutic good should be of a quality demonstrably adequate for the purpose for which it is to be used and should not compromise the quality or safety of the finished therapeutic good. Full details of the pack/kit contents, item specifications and use, demonstrating that quality and safety of the material being collected and handled are not being compromised, should be included in the submitted dossier.

Kits/packs that are supplied outside its manufacturer's governance and used in the treatment of a patient are generally regulated as medical devices, except where the kit or pack is regulated as a medicine (consists of medicines), or the kit does not contain goods regulated by the *Therapeutic Goods Act*.

Even if the pack/kit is not required to be on the ARTG, it is highly recommended that those items contacting the human tissue or donor samples for testing are approved for human use, that is, they are included on the ARTG or are of pharmacopoeial grade.

4.2. Manufacturing process

The section should clearly describe all aspects of the manufacturing process from the transport of the starting material to the manufacturing site to final product release, highlighting compliance with relevant standards when applicable. The process should be carefully designed to ensure product consistency and a risk management approach should be used to inform the in-process controls and specifications.

4.2.1 Manufacturer’s details

Name, address, process steps and TGA GMP licence/certification information should be provided for all manufacturers. At minimum, all manufacturers must have a current GMP licence (under Part 3-3 of the Act) or certificate/clearance (under Part 3-2A of the Act), or provide evidence of an application for a licence to manufacture therapeutic goods in Australia or an application for a GMP certificate for the overseas manufacturers submitted to the Office of Manufacturing Quality. Ideally the information should be presented in a tabulated form and copies of the licence/certificate/application should be included in the dossier.

Manufacturers involved solely in collection of biological starting material or infectious disease testing relating to donor evaluation should be listed in Section 4.1.4 and 4.1.2, respectively.

4.2.2 Description of manufacturing process and process controls

Description of entire manufacturing process, from the completion of the collection of the biological starting material to final product release. This should include an annotated flow diagram, with indication of the critical steps and in process control points. For example, transport of starting material to the manufacturer, cryopreservation, labelling and storage

Reprocessing, if applicable .

Detail microbial control steps.

4.2.3 Control of materials

A list of all critical materials (as defined in ARGB Appendix 14 – Glossary), including excipients, vectors and medical devices used in the manufacturing process.

This 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.

Where the product is not on the Register or a default Standard does not apply, information must be provided to demonstrate control of the quality and safety of the material. The level of control of each material should reflect its use and potential risk to the product. More detail on minimal information required on such materials available in ARGB Appendix 4.

There is provision under the Therapeutic Goods Regulations, Regulation 16 GF for data (e.g. about a critical material) to be submitted directly to the TGA for evaluation, for example where information is in-confidence to the material manufacturer.

The minimal requirements for critical material that are solutions, antimicrobial agents, or material containing any components of human or animal origin, are discussed in ARGN Appendix 4. Additional controls may be expected for substances employed in the manufacture of Class 4 biologicals if there is a likelihood of an impact on the quality, safety or efficacy of the finished biological.

Cell banking should be described in accordance with the guidelines in ICH Q5D and the EMEA document "Note for guidance on the quality, preclinical and clinical aspects of gene transfer of medicinal products".

The use of any vectors or other gene transfer procedures should be described in accordance with the guidelines in the EMEA document "Note for guidance on the quality, preclinical and clinical aspects of gene transfer of medicinal products"

When bovine serum is used, the recommendations of the EMEA document "Note for guidance on the use of Bovine Serum in the manufacture of human biological medicinal products" should be followed. The use of irradiated sera and/or synthetic alternatives is encouraged.

4.2.4 Critical steps and intermediates

A full description, including acceptance criteria, of all critical control points (in-process controls) and key elements as informed by risk analysis should be included. For example, determination of tissue competency prior to freezing, or processing reagent residue.

Quarantine measures for biological starting material until donor testing is complete, or if autologous material is found to be infectious disease positive should be discussed.

Detail 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, a list of organisms tested should be provided, including 'allowed' organisms if positive growth is identified.

4.2.5 Validation of the manufacturing process

Each step in the manufacturing process should be validated. For guidance on methodology that could be utilised refer to ICH Q2R1 "Validation of Analytical Procedures: Text and Methodology"

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

- ISO 11737-1 Sterilization of medical devices – Microbiological methods – Part 1: Determination of a population of microorganisms on products.
- ISO 14160 Sterilization of health care products –Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives – Requirements for characterization, development, validation and routine control of a sterilization process for medical devices.

Where terminal sterilisation is not an option, aseptic process is required and must be validated.

Viral removal/reduction steps must be validated, if performed.

In case of limited sample availability, and where justified, more extensive validation should be performed with samples of comparable characteristics for validation purposes.

4.3. Characterisation

An extensive characterisation of the biological, including biological components, non-biological components, including a profile of any potential toxicities, and the finished product, should be established. This characterisation should be above and beyond the scope of the standard manufacturing in-process controls and release criteria. Characterisation studies should be of the extent that they can facilitate identification of critical quality attributes and, when changes are made to the manufacturing process, 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 do however 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 should be used to inform the final product specifications, in conjunction with characterisation studies and relevant Standards.

4.4.1 Release specifications

Finished product release specifications should 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

All analytical procedures should be listed and copies attached.

Details of all reference standards and material should be provided.

- primary reference material should be established for all critical assays used in the testing of finished product
- where a national or international standard is available, appropriate reference material should be calibrated against it
- where appropriate, a description of the preparation of the reference material and documentation of its characterisation and storage conditions should be provided.

4.4.3 Validation of analytical methods

Each step in the manufacturing process should be validated. For guidance on methodology that could be utilised refer to ICH Q2R1 "Validation of Analytical Procedures: Text and Methodology"

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

- ISO 11737-1 Sterilization of medical devices – Microbiological methods – Part 1: Determination of a population of microorganisms on products
- ISO 14160 Sterilization of health care products –Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives – Requirements for characterization, development, validation and routine control of a sterilization process for medical devices.

Where terminal sterilisation is not an option, aseptic process is required and must be validated.

Viral removal/reduction steps, if performed.

In case of limited sample availability, and where justified, more extensive validation should be performed with samples of comparable characteristics for validation purposes.

4.4.4 Finished product analysis

The ability of the manufacturing process to consistently produce final product within the stated specifications, must be demonstrated.

The number of manufacturing runs analysed to demonstrate process consistency should be stated and justified.

4.4.5 Justification of specifications

The release specifications should be justified. For example, with respect to the relevant Standards, and/or published literature, and/or based on process validation.

4.4.6 Containers

The suitability of the container/s used for the final product must be demonstrated; including information and validation of container type, container and closure material or, where applicable showing compliance to relevant Standards.

4.5. Storage and stability

Biological materials are particularly sensitive to adverse conditions, and as such a full investigation of the stability of the final product, should be carried out, and used to set storage conditions and justify the proposed shelf-life.

Further information is available in ICH Q5C "Stability Testing of Biotechnological/Biological Products".

4.5.1 Stability studies

Include a summary of the stability studies and conclusions. This should be tabulated, showing the time since the commencement of the study against the specific parameters.

All post-approval commitments should be stated, 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

Result tables for all stability studies should be provided here.

4.6. Product development

It is expected that the manufacturing process will undergo a degree of evolution, from the original design phase to that which is currently being performed. For example, the manufacturing processes may be changed as a result of improved technology or increased scale of production. This section does not require documentation of all such changes, but where major studies and/or validations have been performed before a significant change was introduced to the manufacturing process (one that has the potential to alter the function of the final product), it is necessary to determine the validity of these earlier studies. The level of documentation should include, but not be limited to, discussing/demonstrating product comparability.

4.7. Labelling and release documentation

The traceability of the biological material throughout the lifecycle of a biological, from initial donor selection to administration of the biological finished product to the recipient is a critical component of product labelling and documentation. This is achieved by the establishment of a single rational labelling system that allows all users involved in the collection, manufacturing and administration of the biological to use. In addition, the information captured in the final product labels and accompanying release documentation is critical to informing the end user and recipient of the quality, safety and efficacy of the biological.

Compliance with TGO 87 must be demonstrated.

Examples of all unfilled labels, and any accompanying documentation, demonstrating compliance with TGO 87, must be supplied.

Examples should be provided to scale and in colour, where applicable.

The labels must demonstrate traceability of biological material from initial donor and throughout the manufacturing process.

TGO 87 outlines the minimal requirements for the container labels and accompanying documentation, but the use/inclusion of release documentation detailing additional product information, e.g. results of release testing, are encouraged. Copies of these accompanying documents should be provided.

Where bioburden testing identified growth of 'allowed' organisms the release labels should contain this information.

Where infectious disease testing is positive, the release labels should contain this information, and state 'for autologous use only'.

Outer container labels and transport labels should be detailed under Section 4.8 Transportation.

4.8. Transportation

This section covers any 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 should comply with product-specific Standards, local laws and regulations, and be fully validated.

Transportation of the biological at any stage of its manufacturer must be detailed; including transportation of the starting material from the collection site to the manufacturing site, and any transportation between manufacturing sites.

Transportation and packing procedures (including labelling) should be provided and fully validated with respect to temperature and integrity.

5. Non-clinical development

Prior to initiation of clinical trials, it is essential to gain an understanding of the biological dynamics/ kinetics and toxicology of a biological with *in vitro* testing as well as through animal studies. These studies will provide in-depth fundamental biological, pharmacological and toxicological information concerning the biological for human-based clinical trials. The objectives of the non-clinical studies are to demonstrate proof-of-principle, define the biological dynamics/kinetics and toxicological effects predictive of the human response, not only prior to initiation of clinical trials, but also throughout clinical development and application. The goals of these studies include the following:

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

For further guidance on non-clinical data requirements please refer to the relevant EMEA guidelines, for example:

- EMEA *Guideline on human cell-based medicinal products 2008*
- EMEA *Gene Therapy product quality aspects in the production of vectors and genetically modified somatic cells 1995*
- EMEA *Reflection paper on Stem cell based product 2000* for further guidance on quality and manufacturing aspects
- EMEA *Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products 2010*

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. Relevant published studies could be one source of data to support the application. However, very often those published studies are not designed to answer a relevant pharmacological or toxicological question. Studies usually do not contain sufficient information for an independent review (e.g., raw data) or tested product is not immediately comparable to the finished biological. Therefore, adequate pharmacological/toxicological endpoints may not have been incorporated into the design of the studies and results are not readily applicable to the biological. Nevertheless those published studies may well be complementary to unpublished studies designed specifically for the biological to support the application.

5.1. Biological dynamics and kinetics

Non-clinical studies in a suitable model *in vitro* or *in vivo* should be adequate to demonstrate the proof of principle of the biological with the principle effects identified. Once demonstrated, further studies examining potential undesirable physiological effects of the product including their bioactive products should be investigated in an appropriate animal model. Safety pharmacology (e.g., cells may secrete pharmacologically active substances), should be considered on a case-by case basis depending on the characteristics of the product. Conventional absorption, distribution, metabolism and excretion studies are usually not relevant for biologicals. However, kinetics, migration and persistence studies should be performed to

demonstrate tissue distribution, viability, trafficking, growth and phenotype and any alteration of phenotype due to factors in the new environment. Cells may migrate within the host, thus presenting clinical concerns regarding adverse reactions. This should be evaluated in animals using appropriate methods (with appropriate ethics approval). For cell-based products that produce systemically active molecules, the distribution, duration and amount of expression of these molecules and the survival and the functional stability of the cells at target sites should be investigated. Finally the applied biological may interact with surrounding cells and tissues and those interactions should be examined.

- Proof of concept/principle studies *in vitro* and/or *in vivo*
- Studies examining potential undesirable physiological effects of the product in an appropriate animal model
- Safety pharmacology studies on a case-by-case basis
- Kinetics, migration and persistence studies
- Interactions studies examining the interaction of the applied tissue/cells or its surrounding tissue with the non-cellular structural components and other bioactive molecules as well as the integration of the product with the surrounding tissue.

5.2. Toxicology

Toxicity may occur, for example, due to unknown cellular alterations developed during the manufacturing process such as altered excretion patterns and *in vivo* behaviour due to differentiation of the cells. Other potential factors that may induce toxicity include the presence of components that are used in the manufacturing process or are part of a structural component, or proliferation of the applied cells in an unwanted quantity or in an unwanted location. 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 be appropriate or feasible, the scientific justification for the models used, or the omission of studies, should be provided. There are a number of additional toxicological issues that need to be considered including, but not limited to, immunogenicity, auto-immunity and tumorigenesis. The need for genotoxicity, developmental and reproductive toxicity studies should be considered on a case-by-case basis. In general, non-clinical studies should include the following:

- 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.

6. Clinical development

Human-derived cell and tissue therapies present novel challenges in clinical development programs. Such products are heterogeneous in origin and type of cells, may be of autologous or allogeneic origin, and can be self-renewing stem cells, committed progenitor cells or terminally differentiated cells which have a specific physiological function. They may be expanded ex-vivo, induced to differentiate along a particular pathway, or genetically modified. They may also be used alone, associated with biomolecules or other chemical substances, or combined with structural materials.

In general, when a human-derived cell or tissue therapy product enters the clinical development phase, the same requirements as for other medicinal products will apply. However, due to the specific biological characteristics of such products, alternative approaches to Phase I to III clinical trials may be necessary and, with justification, will be acceptable for clinical development. Relevant non-clinical studies, previous clinical experience of the treated pathology, and initial clinical studies may be useful for demonstration of 'proof of principle', provided there is an appropriate choice of clinically meaningful endpoints for safety and efficacy evaluation.

Human-derived cell and tissue therapies may require administration via specific surgical procedures or methods of administration, and may need to be combined with other treatments to obtain the intended therapeutic effect. Biological effects are highly dependent on the *in vivo* environment, and may be influenced by the replacement process or immune reaction either from the patient or from the product. Such requirements arising from clinical development programs must be taken into account for the final use of products. Standardisation and optimisation of the therapeutic procedure as a whole, including the method of administration and required concomitant medication such as immunosuppressive regimens, should be an integral part of clinical development studies, and this should be fully described in the product information provided.

A risk-based approach will be used to determine the extent of data required for marketing approval for Class 3 and Class 4 products, based on the identification of risk factors inherent to the product in question, and associated with its quality, safety and efficacy. This should be clearly distinguished from Risk Management, which is addressed in 6.7.

TGA guidelines will be developed to inform this risk-based approach, and it is proposed that there will be separate sections on aspects specific to cell and tissue-based products (mostly expected to be Class 3) and gene therapy products (Class 4) respectively. It is not intended that this will provide a rigid classification system of different risks, but will clarify the concept by using examples with different risk profiles.

EMA/CHMP has recommended drafting of a guideline on the application of the risk-based approach for human-derived cell and tissue products (EMA/CHMP/CPWP/708420/2009). This recent concept paper includes a non-exhaustive list of risk factors for cell-based and gene therapy biological products which may be useful for manufacturers/sponsors in identifying and developing discussion regarding justification of the extent of quality, non-clinical and clinical data presented for marketing authorisation. Depending on the risk of the product, it is envisaged that some sections of the application dossier may be emphasised or complemented with additional data where necessary, or alternatively limited when appropriately justified on the basis of risk.

The diversity of human cell-based products can lead to very different levels of risk to patients, medical personnel or the general population. Therefore, development plans and evaluation requirements will need to be adjusted on a case-to-case basis, according to a multifactorial risk based approach. Early consultation with TGA is therefore strongly recommended with regard to uncertainties in the rationale of clinical development programs, including confirmatory studies, for products for which marketing authorisation may be sought.

Requirements for clinical evaluation are intended as guidance for human-derived cell and tissue products for which application for inclusion of the biological is being made, but these principles should also be considered for products entering into clinical trials.

These requirements are based on European Medicines Agency (EMA) guidelines, as set out in the following source documents:

- EMEA/CHMP Guideline on Human Cell-Based Medicinal Products (EMEA/CHMP 410869/2006)
- EMEA/CHMP Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products (EMEA/CHMP 149995/2008)
- ICH M4E Common Technical Document for the Registration of Pharmaceuticals for Human Use – Clinical Overview and Clinical Summary of Module 2. Module 5: Clinical Study Reports (CHMP/ICH/2887/99 Rev 1 Efficacy)
- EMEA/CHMP Concept Paper on the Development of a Guideline on the Risk-Based Approach according to Annex I, Part IV of Dir. 2001/83/EC applied to Advanced Therapy Medicinal Products (EMA/CHMP/CPWP/708420/2009).

6.1. Biodynamics

Even where the mechanism of action is not understood in detail, the main effects of the biological should be known.

Where the purpose is to correct the function of deficient or destroyed cells or tissues, functional tests should be undertaken.

If the intended use is to restore or replace cells or tissues, with an expected lifelong functionality, structural or histological assays may be potential biodynamic markers. These might include, but are not limited to, microscopic, histological or imaging techniques, enzymatic activities, expression of cellular antigens, proteomics and functional genomics analysis.

Where a non-cellular component is combined with a human cell-based product, the combination should be assessed clinically for compatibility, degradation rate and 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 should 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 considered necessary, the schedule should be addressed in terms of the expected *in vivo* life span of the human cell-based product.

6.3. Dose finding studies

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

Where dosage is individualised for the intended recipient (e.g. cell mass density per body weight, volume of missing tissue, missing surface area), the dose to be tested in the confirmatory trial should be supported by the evidence provided in Phase I/II studies.

Phase I/II studies should be designed to identify a Minimal Effective Dose, defined as the lowest dose to obtain the intended effect, or an Optimal Dose Range, defined as the largest dose range required to obtain the intended effect based on the clinical results for efficacy and tolerability.

If possible, the Safe Maximal Dose should also be investigated, defined as 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 should be adequate 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 should 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).

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 should be capable of detecting common adverse effects.

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

The risk of the therapeutic procedure as a whole should be evaluated and used to justify the clinical studies and the choice of the target patient population.

All safety issues from the preclinical development program should be addressed, especially in the absence of an animal model of the treated disease or in the presence of physiological differences limiting the predictive power of ahomologous animal model

Particular attention must be paid to those 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 and concomitant treatment.

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

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

6.6. Biovigilance and risk management plan

Routine biovigilance and traceability of the biological should be described in a Risk Management Plan (RMP), based on the considerations outlined in the EMEA/CHMP Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products (EMEA/CHMP 149995/2008):

- 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 and the *in vivo* durability of any associated medical device/biomaterial component, which must be addressed in the RMP
- Specific requirements linked to the biological characteristics of the cell-based product may require special bio-epidemiological studies
- Traceability in the donor-product-recipient axis, or in the product-recipient axis for autologous products, is required in all circumstances.

7. Appendices

Appendix 1 Summaries of compliance with standards

For TGO 87 and the relevant product-specific TGOs, tables are provided within their guidance documents that indicate where individual clauses should be documented in the main dossier. In addition, these tables contain a column where a summary of the information included in the dossier to address that individual clause must be provided. These tables should be completed, printed and placed in this Appendix.

Appendix 2 References

Copies of all papers used as supporting evidence or/and to justify any specifications must be provided. All other references should be listed only.

Appendix 3 Supplementary dossier information (where applicable)

(a) Does this application depend upon the outcome of, or relate to, any other application currently under evaluation by TGA? If YES, please provide submission number(s) and/or TGA numbers.

(b) Does the submission make reference to 'in confidence' data submitted by manufacturers directly to the TGA for evaluation; such as a information on the manufacture of a critical material, a Drug Master File (DMF), a Plasma Master File (PMF), a Biological Master File (BMF) or to an EDQM Certificate of Suitability (CEP)? If so, the applicant must provide in writing permission from the owner of the confidential information allowing the TGA to access that information on behalf of the applicant.

(c) If there were any pre-submission meetings, please detail agenda, conclusions and contact person and attach any pertinent emails, minutes from meetings, letters etc.

(d) Is there any other pertinent information that would assist the TGA with the evaluation of the dossier, for example planned changes to the contact person or planned changes to company details.

Appendix 4 Overseas regulatory information (where applicable)

(a) Please detail the commercial history, including date of first clinical application of the product and the marketing in each country other than Australia.

(b) Please detail the regulatory status in each country other than Australia, including approvals, rejections, severe adverse reactions linked to the product and recalls.

(c) To establish that the overseas manufacturers of the goods are of an acceptable standard, is there one or more overseas manufacturer of the goods for which GMP clearance letters from the TGA have not yet been obtained or requested?

(d) Do you give approval for the exchange of evaluation reports with other regulatory agencies for this submission?

8. References

Resource	URL
TGA website	https://www.tga.gov.au
TGA blood and blood components information	http://www.tga.gov.au/blood-and-blood-components
EMEA document "Guideline on human cell-based medicinal products"	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003894.pdf
ICH Q2R1 "Validation of Analytical Procedures: Text and Methodology"	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf
ICH Q5C "Stability Testing of Biotechnological/Biological Products"	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5C/Step4/Q5C_Guideline.pdf
EMEA's Guideline on human cell-based medicinal products 2008	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003894.pdf
EMEA Gene Therapy product quality aspects in the production of vectors and genetically modified somatic cells 1995	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003449.pdf
EMEA's Reflection paper on Stem cell based product 2010 for further guidance on quality and manufacturing aspects	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500079932.pdf
EMEA Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products 2010	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070031.pdf
EMEA risk-based approach for human-derived cell and tissue products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500069264.pdf
EMEA/CHMP Guideline on Human Cell-Based Medicinal Products (EMEA/CHMP 410869/2006)	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003894.pdf

Resource	URL
EMEA/CHMP Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products (EMEA/CHMP 149995/2008)	http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006329.pdf
ICH M4E Common Technical Document for the Registration of Pharmaceuticals for Human Use – Clinical Overview and Clinical Summary of Module 2. Module 5: Clinical Study Reports (CHMP/ICH/2887/99 Rev 1 Efficacy)	http://www.tga.gov.au/docs/pdf/euguide/ich/ctdm2efficacy.pdf - page not found http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002723.pdf
EMEA/CHMP Concept Paper on the Development of a Guideline on the Risk-Based Approach according to Annex I, Part IV of Dir. 2001/83/EC applied to Advanced Therapy Medicinal Products (EMA/CHMP/CPWP/708420/2009)	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500069264.pdf
EMEA/CHMP Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products (EMEA/CHMP 149995/2008)	http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006329.pdf
ISO (International organisation for standardization)	http://www.iso.org/iso/home.html
ICH Q5D Derivation and characterisation of cell substrates used for production of biotechnological/biological products	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5D/Step4/Q5D_Guideline.pdf
EMEA document "Note for guidance on the quality, preclinical and clinical aspects of gene transfer of medicinal products" CPMP/BWP/3088/99	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003987.pdf
Note for guidance on the use of Bovine Serum in the manufacture of human biological medicinal products CPMP/BWP/1793/02	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003675.pdf

Version history

Version	Description of change	Author	Effective date
V1.0	Original	BSS	June 2011
V1.1	Updated dossier requirements for electronic submission. Included link to guidance on Biovigilance responsibilities of sponsors of biologicals	BSS	March 2018

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

D18-10235144