Australian Government
Department of Health
Therapeutic Goods Administration

Australian Regulatory Guidelines for Biologicals

Appendix 4 – 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

Version 2.0, February 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

Version history

Version	Description of change	Author	Effective date
V1.0	Original Publication	Biological Science Section/Office of Scientific Evaluation	June 2011
V1.1	Internal references amended	Biological Science Section	29 August 2011
V2.0	Removal of information duplicated in TGO 88 and an update to improve guidance	Biological Science Section	13 February 2014

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Background

This document provides guidance to Therapeutic Goods Order No. 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 (TGO 88).

These requirements are to be applied in conjunction with the revised Code of Good Manufacturing Practice for human blood and blood components, human tissues and human cellular therapy products, 2013 (cGMP) and replace the current Code of Good Manufacturing Practice for blood and tissues (2000).

Applicable products

TGO 88 is a standard applicable to:

- human blood and blood components including:
  - red cells
  - white cells
  - platelets and
  - plasma (including plasma for fractionation)
- human tissues and
- human cellular therapy products (including haematopoietic progenitor cells)

Additional and alternative requirements

The standard specifies the minimum criteria to minimise the risk of infectious disease transmission through the above mentioned therapeutic goods. Additional or higher requirements can be included at a sponsor's discretion or may also be required by a product-specific order or default standard. Further testing as clinically relevant for specific products or patient populations may also be necessary, for example Cytomegalovirus testing where recipients are children or immunocompromised. This guidance also includes a number of references to 'current Therapeutic Goods Order made under section 10 of the Act'. Where specified, this permits the application of alternative requirements from the TGO for a specific product type, recognising that a 'one size fits all' approach may not be appropriate in some circumstances. It may also be appropriate for a manufacturer to apply more stringent requirements for a specific product, for example by performing additional tests not specified in TGO 88 on the donor or product.

The TGA accepts that alternative approaches may be suitable provided there is appropriate justification. Where alternative approaches are used these must be validated by the manufacturer. This justification and supporting validation information is subject to TGA review and approval. It must be provided in the data supporting the application for product approval or in an application for a variation, post approval.

Terminology

The terminology in TGO 88 and this guidance refers to starting materials (i.e. the collected material) as 'blood, blood components, cells and tissues' as distinct from the finished

therapeutic good, which is described as 'product' or 'blood, blood component, tissue or cell therapy product'.

Presentation of dossier information

Annex 1 of this guidance includes a reference table to assist the applicant determine the possible locations for information provided in a dossier submitted in support of an application for a biological. Sponsors of blood component products who need to submit a Technical Master File (TMF) demonstrating compliance to TGO 88 should amend the table to reference the specific sections of their TMF.

Information should be submitted in the indicated sections of the application to demonstrate that the requirement has been met. In addition, the table should include a short statement indicating how the requirement is met. Please note that the TGA will evaluate the entire application, so only a brief statement is required.

Review of TGO 88

TGO 88 will be subject to review on a regular basis, as changes in technology, and best practice, requires. Sponsors and manufacturers are encouraged to discuss with the TGA any changes in standard practice or evolving technologies that may affect, or be affected by, the requirements of TGO 88.

Enquires can be sent to the Biological Sciences Section of the TGA via email to bloodandtissues@tga.gov.au.

Part 1 Introduction

Section 3 (of TGO 88) transition

TGO 88 commenced on 31 May 2013. There is a 12 month transition period to meet the requirements of TGO 88, which finishes on 31 May 2014.

Sponsors and manufacturers of human blood, blood components, tissues and cellular therapy products who wish to do so may begin complying with TGO 88 before 31 May 2014, but must also ensure that the revised cGMP is or has been observed in the manufacture of their goods, as these are intended to be applied together.

Human blood and blood components, human tissue and human cellular therapy products both collected and released for supply prior to 31 May 2014 (or the time of elected compliance with TGO 88 and cGMP) are exempt from this order.

Section 5 Interpretation

This section provides definitions of the terms that are used within TGO 88. The definitions provided within TGO 88 are specific to the Order and are not intended to apply outside of TGO 88.

Where possible, definitions are derived from current TGA legislation, international regulatory documents or current industry guidance documents. Where a suitable definition has not been identified by those means, the TGA has developed a definition that is informed by equivalent terms used in the aforementioned documents.

Some definitions, such as the definition of 'microbial', have been informed by the Therapeutic Goods Committee Subcommittee on Biologicals (TGC subcommittee) or in the case of 'specified microorganism', informed through public consultation.

The definitions form a part of a glossary that is located in Appendix 14 of the Australian Regulatory Guideline for Biologicals (ARGB). Further clarification on a subset of these definitions is provided below:

- **Allogeneic use:** this definition intends to capture all non-self transplantation or transfusion, and includes syngeniec use (i.e. between identical twins).
- **Asystole:** this definition includes cross-clamp time, which for organ donors refers to the time that the aorta is cross clamped by a surgical team. The time of certification of circulatory death would also be considered appropriate if the tissue donor is also a solid organ donor.
- **Cornea only donor:** this definition recognises that products collected for corneal transplantation may include the cornea as well as surrounding ocular tissue; however, the cornea will be isolated as part of the operative procedure prior to transplantation. The testing requirements for cornea differ to those for other ocular tissue.
- **Critical material:** the cell or tissue product itself is not included in the definition of critical material. This is the term used for supplies or reagents that come in direct contact with the cell or tissue during any stage of manufacture, such as primary containers or collection kits. Equipment that is used in the manufacturing process such as centrifuges is not a critical material. Compliance with the requirements for substances used in collection and manufacture, including critical materials, must be demonstrated in the relevant section of the product dossier.

- **Risk of prion disease:** this definition is consistent with the recommendation from the Australian Health Ministers' Conference in 2003 and is consistent with the deferral criteria applicable for blood donors. Further information on assessing the risk of prion disease can be found on the TGA website. Further considerations for the risk assessment may be informed by the World Health Organisation (WHO) categorisation of risk tissue types, European Union (EU) guidelines, European Medicines Agency (EMA) guidance and Food and Drug Administration (FDA) guidelines. 'Iatrogenic' refers to potential exposure through the consumption of, or treatment with, potentially contaminated product e.g. beef products, bovine insulin, blood transfusion or tissue transplantation.

- **Specified microorganisms:** where products are derived from starting materials have an inherent level of microorganisms, such as skin, the sponsor should develop a list of specified microorganisms of clinical significance, which, if isolated, require rejection of the product for clinical use. This process should be based on a risk assessment and consider the category of tissue, the method of processing and the nature and type of microorganisms that might be present. The definition does not mandate a requirement to test for rickettsia or mycoplasma, but these may be considered significant organisms for particular starting materials.

- **Quarantine:** products and samples must be segregated from the mainstream inventory until the product has been determined to be compliant with all necessary requirements or release criteria, e.g. where infectious disease test results may not be complete. This is especially relevant for products stored in an inventory (or banked) with other products for potentially long periods of time as these products pose a risk of transmission to other products through physical contact, and a risk to the public from unintentional release and use. Quarantine procedures are assessable under the cGMP. Quarantine practices should be determined based on risk; however, the conditions of quarantine should be consistent with storage conditions wherever possible.

- **Physical assessment:** examples of the considerations that may inform the physical assessment are provided in Section 11, but additional considerations should be determined on the basis of the product type and intended use.

Part 3 Specific requirements

Section 9 - Medical and social history of prospective donors

This section specifies the minimum standards for assessing the suitability of a donor. The medical and social history is the first tier of risk minimisation in terms of infectious disease transmission, as high risk donors can be identified before donation, or where allowed, after donation but before introduction of the product into the mainstream inventory of the manufacturing facility.

Subsection 9(1)(a) Living donor interview

In the case of living donors, a face-to-face interview is preferred, but it is recognised that this may not be possible within the specified timeframe. Where a face-to-face interview is not conducted, the alternative process should be described.

Subsection 9(1)(b) Living donor interview timeframes

Obtaining preliminary information without a trained interviewer prior to interview may be acceptable, but confirmation of information/ currency of donor history must be in the presence of a trained interviewer (as defined) within 30 days of collection and must be completed before product is released from quarantine. To ensure the relevance of the information collected, the timeframes around when the donor interview is performed should be as close to the collection date as feasible.

Subsection 9(2)(b) Deceased donor medical and social history

For deceased donors, it is recognised that the next-of-kin (knowledgeable historian) may not be available for interview within the required timeframe and therefore donor documentation may provide the necessary evidence to obtain the donor history within the specified timeframe.

Subsection 9(3), 9(4) 9(5) & Table 1 Donor medical and social history

Where possible and practicable these criteria and deferral periods are harmonised with international criteria.

Table 1(b) Suspected viral infections

An uninfected state can only be established if serological (HIV/HCV/HTLV) and NAT (HIV/HCV) testing is carried out on a blood sample, collected beyond any window period, and a negative result is obtained.

Table 1(c) HBV deferrals

Demonstration of immunity to Hepatitis B (HBV) would be determined by a testing algorithm that is informed from evidence in scientific literature or other reliable sources.

Donors suspected of being infected with HBVwho are HBsAg negative are considered to be ‘immune’ if both of the following are true:

- They have an antibody titre to HBsAg at a level greater than or equal to 100 IU/L (or 100 mIU/mL), and
- HBV NAT test is negative

Donors suspected of being infected with HBV who are HBsAg negative are considered to be 'not exposed' if they test negative for antibodies to HBsAg and test negative by HBV NAT.

Where serology tests are repeated 180 days after donation it is possible to replace the NAT requirements discussed above.

For HBsAg negative persons who are demonstrated to be immune or never exposed, no ineligibility period applies.

Table 1(d) non-medical drug injections

The term 'non-medical reason' refers to procedures such as recreational drug use or cosmetic procedures that are not undertaken by a registered healthcare provider. This deferral criterion is not intended to apply to individuals that have participated in clinical trials.

Table 1(f) risk of prion disease

The term 'risk of prion disease' is defined in TGO 88 and further guidance is provided under Section 5 of the TGO. Other situations where permanent deferral of a donor may need to be considered due to risk of prion disease include where patients have symptoms of progressive neurological disease consistent with prion disease, and where activities that could iatrogenically transfer prion disease have occurred. One example is a donor who has ever had an allogeneic human tissue transplant such as cornea or dura mater.

Table 1(g) human pituitary-derived hormone

It is recognised that human derived pituitary hormone is currently not available in Australia and that synthetically-derived product is currently used. The ineligibility does not apply to potential donors that have received synthetically-derived product.

Table 1(i) and (j) allogeneic products

If donors have received allogeneic blood, blood components or human derived clotting factors, organs, cells or tissues, the sponsor must provide evidence that the product the donor received is compliant with TGO 88. This may take the form of a statement describing the international standard with which the product was compliant and confirming equivalence to TGO 88. Where differences are identified between the quality of the overseas product and the requirements outlined in TGO 88, a risk assessment approach should be taken to determine if the donor should be deferred or whether equivalence to TGO 88 could be justified.

Table 1(k) sexual practices

Sexual practices that are considered to increase the risk of acquiring infectious diseases that can be transmitted by blood, cells or tissues include, but are not limited to: sexual activity with a sex-worker, sexual activity with someone who uses intravenous drugs, having a partner who lives or lived in a high HIV risk country. The donor information that informs this deferral should be determined based on risk as relevant to the nature of the product and its use and must be provided in the relevant section of the product dossier.

Table 1(n), (o), (p) and (q) risk of malaria

Endemic areas for malaria are published on the World Health Organisation or Centers for Disease Control and Prevention websites. The definition of endemic area may be at the country level, or it may be possible to justify more specifically 'local areas' within a country.

Table 1(p) visit to a malaria endemic area

The term 'visit' is to be applied as consistent with WHO guidelines. In the case of malaria, visitation includes any situation where the donor has been potentially exposed to the external environment. For example, it would not include a stop-over in an airport terminal where the individual did not leave the terminal, but would include if the donor were to travel to another location (including another terminal) in a bus or private taxi. Malarial prophylaxis does not affect the malaria exclusion periods; unless the use of the specific drug deems the donor ineligible under provisions included under subsection 9(12).

Table 1(q) undiagnosed febrile illness

The decision to apply this deferral criterion must be based on clinical judgement as to whether the febrile illness is consistent with malaria.

Table 1(r) active infection

A list of infections that are relevant to the product and warrant deferral should be established. Determination of a disease free state should include an algorithm and at minimum the essential assays or parameters to demonstrate that an infection has cleared or will render the target cells or tissue unsuitable for manufacture.

Table 1(s) epidemiological situations

This deferral is intentionally broad to encompass unforseen infectious disease risks, for example a Hepatitis A epidemic, or other emerging or re-emerging infectious disease outbreak. It is the responsibility of the sponsor to demonstrate that a process is in place to satisfactorily monitor, assess and action epidemiological situations relevant to their products. In response to an alert situation appropriate deferral criteria must be established; usually in consultation with the TGA. The TGA must be notified of the deferral parameters that are applied in epidemiological situations, and the change may need approval prior to implementation.

Subsection 9(6) Exemption for plasma for fractionations

This subsection provides specific exemption from certain donor history criteria and deferrals for plasma for fractionation.

'Plasma for Fractionation' is defined in Ph Eur monograph 0853 as the liquid part of human blood remaining after the separation of the cellular elements from blood collected and is intended for the manufacture of plasma-derived products.

Subsection 9(9) Vertical transmission of infectious disease

This subsection provides specific criteria that apply to the mothers of infant donors in order to reduce the risk of vertical transmission of disease via placenta or lactation. Compliance with this clause should also consider circumstances where an infant donor may have received milk from a donor milk bank, in which case the donor of the milk should also be assessed.

Subsection 9(12) Exemptions for non-live vaccine deferrals

This subsection specifies that vaccination with non-live vaccines is not required to be deferred (provided all other criteria are met). The types of vaccines covered by this statement would include, but are not limited to:

- Capsular polysaccharide typhoid fever vaccine;

- Vaccines with inactivated viruses e.g. flu vaccines;
- Toxoids;
- Diphtheria and tetanus vaccines;
- Hepatitis A and Hepatitis B vaccines unless vaccination was administered as a protection in the case of a recent exposure, if no exposures have occurred, or until a disease-free state can be established;
- Rabies, tick-borne encephalitis (where no recent exposures have occurred);
- Meningococcal vaccine;
- Subunit vaccines e.g. human papilloma vaccine

Subsection 9(13) Donors with a known condition

This subsection recognises that diseases and pathological conditions that are not required to be screened by this standard (non-infectious diseases) might be relevant to the safety or quality of the product or that donor medical treatment prior to collection may adversely affect the product. The criteria would depend on the product type and the intended use of the product, for example:

- tissues exposed to irradiation
- diseases that affect joint integrity in musculoskeletal donors
- immunodeficiency disorders or use of immunosuppressive agents in patients with a consequent higher risk of asymptomatic opportunistic infection
- reactivation of past infection
- situations that could impair the ability of testing to detect infection e.g. hypogammaglobulinaemia and HCV antibody testing.

These requirements allow for the Sponsor to specify additional criteria that may be applicable based on clinical justification. The subsection does not exclude donors who have recently received a vaccine not mentioned in Table 2, as long as they did not present with any adverse reactions (including allergic reactions).

Other relevant conditions include e.g. hypertension and pregnancy.

Section 10 Donor blood sampling, test kits, test protocols and test management

This section specifies the minimum standards for samples and test methods used for infectious disease testing. Quality of the samples and validation of the methods used in donor testing is critical for determining donor suitability.

Subsection 10(2) Living donor blood sampling

This subsection specifies the timeframes for collecting donor samples. The 7 day window for living donors is based on current international requirements and represents the nominal timeframe to collect samples to accurately reflect the donor infectious disease status. It may be appropriate for manufacturers to apply more stringent timeframes to some cell or tissue types, such as fresh blood. Alternatively, specific products may require more generous timeframes and this would be specified in the respective product TGO. For

example, donor screening for HPC products may be required to be undertaken more than 7 days prior to collection, where recipient myeloablative chemotherapy conditioning commences seven days prior to transplant. The respective TGO specifies that donor samples should be obtained within 30 days prior to collection.

Subsection 10(3) Deceased donor blood sampling

The quality of the cadaveric blood sample must be suitable to allow infectious disease testing to be performed. Instructions for use provided with a test method may define the appropriate time frame for collection of the blood sample prior to testing, or the appropriate time frame should be validated.

Subsection 10(4) Timeframe for testing of donor samples

Timeframes for sample testing and review of results are specified to minimise the risk of introducing an infectious product into the routine processing operations of the manufacturing facility.

Subsection 10(5) Blood sample testing methodology (haemodilution factor)

The results of infectious disease testing may be affected where a potential donor may have recently received an intravenous treatment, for example infusion of blood components, colloids or crystalloids.

For infectious disease test screening protocols, it is recommended that a complete haemodilution assessment be undertaken on all living and deceased donors. Guidance on plasma dilution, including a plasma dilution algorithm and worksheet, is available in the FDA document *Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation*. Other appropriate algorithms may be used, but must be justified.

- If the infusion or transfusion volume for the donor totals more than 2000 mL then it is considered essential that a haemodilution assessment be performed, if;
  - An infusion or transfusion of blood or colloids was received within 48 hours preceding collection of the sample or within 48 hours preceding death, whichever occurred earlier
  - An infusion of crystalloids was received within one hour preceding collection of the sample, or within one hour preceding death, whichever occurred earlier
  - A combination of blood, crystalloids and/or colloids was received within the applicable time frames set out in paragraphs (a) and (b) in the section
- It is also considered essential that an assessment be performed where there have been any infusions or transfusions that might affect test results in a child of less than 12 years of age. The time frames are as defined above
- The date and time of sample collection should be recorded
- An appropriate algorithm must be used to evaluate that plasma dilution and show that it is not sufficient to affect the test results. The plasma dilution factor should be less than 50 per cent, i.e. if greater than 50 per cent dilution has occurred then the post-transfusion/infusion specimen should not be used
- When performing the algorithm:

- Consider volumes of medications administered with IV fluids
- If unknown what volume was administered, consider the worst-case scenario that all was given.

Subsection 10(6) Infectious disease blood sample testing methodology/kits

Each test kit/methodology used for the mandatory donor screening tests and confirmatory tests (if these support final product release) should be validated for the purpose for which it is to be used (intended use) and used in accordance with the test kit instructions. Where test methods are used beyond the test kit instructions, e.g. use on cadaveric samples, validation to support the extended use must be demonstrated.

Subsection 10(6)(a) Technology/methodology of testing kits/methods

The most appropriate technology/methodology shall be determined and justified by the sponsor. The infectious diseases test screening protocol could be an 'in-house' test or a commercial kit and may be conducted by the sponsor or a contract laboratory. The sponsor should also consider utilising new test methods, such as more sensitive assays, as they become available.

In addition, when testing a sample of cadaveric blood the screening test must be specifically approved for use on cadaveric specimens or validated for this purpose by the testing laboratory.

Subsection 10(6)(b) Approval of test kits

If the test kit and methodology has current approval by the relevant regulatory authority in the country where the testing is performed, the evidence of this approval should be provided.

Where test methods are used beyond the level approved by the local regulatory approval, e.g. use on cadaveric samples, validation to support the extended use must be demonstrated. Guidance on performing studies to support modifying the intended use of a test kit to include testing of cadaveric blood specimens to screen donors of human cells, tissues, and cellular and tissue-based products is published by the FDA.

The TGA proposes to utilise this guidance in the assessment of any submitted validation data. This guidance is designed specifically to ensure that a well characterised assay already established for blood donors can be used for testing cadaveric specimens. Alternative methods to characterise a cadaveric assay may be acceptable to the TGA and the supporting validation data should be provided to TGA for review with the application.

Subsection 10(6)(c) Testing facility

All facilities performing donor testing must be approved by the regulatory authority in the country where the testing is performed. For domestic facilities a TGA licence will be required; and for overseas testing facilities the sponsor must hold a TGA clearance demonstrating compliance with GMP requirements. Where confirmatory testing is utilised to decide suitability of a donor, the facility's GMP must include this purpose.

Subsection 10(6)(d) TGA acceptance of testing kits/methods

Sponsors are encouraged to contact the TGA in regards to the acceptability of test kits.

Test kits used in Australia for donor screening should meet the requirements of the In vitro diagnostics (IVD) regulatory framework. Testing facilities in Australia would also need a GMP licence from the TGA.

For test kits used overseas, sponsors are encouraged to contact the TGA in regards to kit acceptability. Sponsors using overseas testing facilities are required to have a TGA clearance for the site.

Subsection 10(9) Archiving samples

A donor blood sample (plasma or serum) must be archived for a minimum of two years after the expiry date of the product, unless otherwise required in another TGO; however, circumstances that would be considered as justification for a failure to archive or maintain a sample may include:

- low sample volume
- breakage and loss
- the sample is used up by relevant testing.

Failure to store a sample or loss of sample is a 'non-conformance' and should follow internal non-conformance procedures. This may be subject to review during GMP inspection.

Subsection 10(11) Retention of test records

The retention of records is required by TGO 88 and is consistent with the requirements of the cGMP. The period of retention must take into account jurisdictional or hospital policies. The application should specify and justify record retention periods and include consideration of product risk, shelf life of product, and timeframe for which the product is expected to have a therapeutic or physiological function in the recipient. Records can be kept in paper or electronic form and be available to inspectors.

Section 11 Donor physical assessment and testing

This section specifies the requirements for the physical assessment of donors and the minimum donor infectious disease testing requirements.

In addition to the medical and social history of the donor, assessment of donor blood samples and the physical assessment of the donor are further key determinants of donor acceptability. Assessment and testing of donors are critical tiers of risk mitigation for infectious disease transmission as the outcomes provide evidence of donor and product safety.

Subsection 11(1) Potential donor testing for infectious diseases

Donor groups for the purpose of section 11 are categorised based on the testing requirements outlined in section 11. The donor groups, as specified in Table 3, are

- deceased donors, with reduced testing for cornea only donors and,
- living donorswith different testing requirements for allogeneic donors and autologous donors.

Subsection 11(2) Donor physical assessments

'Physical assessment' is defined in Appendix 14 of the ARGB. It is the view of TGA that the requirements for physical assessment of a potential donor of blood, cells and tissues must be determined by each individual collection facility according to a risk assessment for the tissue(s) or cells to be collected. The exact nature of this assessment is not prescribed, but it is emphasised that the assessment must be sufficient to 'determine suitability of the person to be a donor'. The requirements will be influenced by the type of product and by the constraints of the clinical requirements of different patient (recipient) groups.

The time periods during which donor physical assessment should occur were specified after consultation with the sector, in order to allow for the assessment to take place at a convenient time prior to surgical procedures but be sufficiently current to allow determination of acceptability of the collection. The process must be appropriately documented. Requirements for performing and documenting the physical assessment must be specified in the dossier submitted by the Sponsor to TGA for evaluation and approval. Some provisions for post-collection assessment have been made in product-specific orders.

The term 'trained assessor', or 'trained interviewer', denotes a person who has undergone training in the specific assessment and consent procedures required by the manufacturer and who has a formal relationship with the manufacturer for this purpose. The requirement for a trained assessor implies that the person undertaking the assessment has an adequate level of training and clinical skills appropriate to the particular assessment being undertaken, and fully understands the requirements for donor evaluation to determine suitability. The assessor need not be a staff member of the manufacturer as long as adequate training has been confirmed.

In addition, there is no prescriptive description as to what entails 'training', but it is required that the manufacturer ensures that the person performing the assessment has an appropriate level of expertise and is familiar with the manufacturers requirements for donor acceptance. The process for training must be documented in the dossier.

Subsection 11(3)(a)(i) Non-reactivity of blood sample tests

The term 'non-reactive' is intended to include other terminology for the same test result such as 'negative' and 'not detected'.

The decision as to which test results lead to a 'reactive' or 'non reactive' test should be justified. In addition the role of any confirmatory testing in the determination of meeting this requirement should also be justified. If any test required by 11(3)(a)(i) is reactive, blood, blood components, cells and tissues must not be collected from the donor.

The policy for determining the individual infectious disease status based on test results must be documented. For example, HBV testing algorithms required to interpret the status of the donor e.g. NAT positive/serology negative or NAT negative/serology positive results.

If the test result for syphilis is reactive by a non-specific test there are two options:

- discard product; or
- perform a specific confirmatory test to rule out the positive result from the non-specific test (non-specific (reaginic) syphilis tests are prone to false positive results).

Subsection 11(3)(c) deceased donor testing in accordance with Table 3

The testing requirements for deceased donors of cornea only tissue are described in column 3 of Table 3. The definition for cornea only donor can be found in Section 5 Interpretation.

Subsection 11(4) serology/NAT testing of blood samples

Initial serology and, where applicable, NAT testing on the sample collected at the time of donation must be undertaken during the timeframe specified in subsection 10(4).

There are two main infectious diseases testing options:

1. for blood, cells or tissues the mandatory requirements for initial sample serology as well as its initial sample NAT testing for HIV, HCV and HBV, can be performed, OR

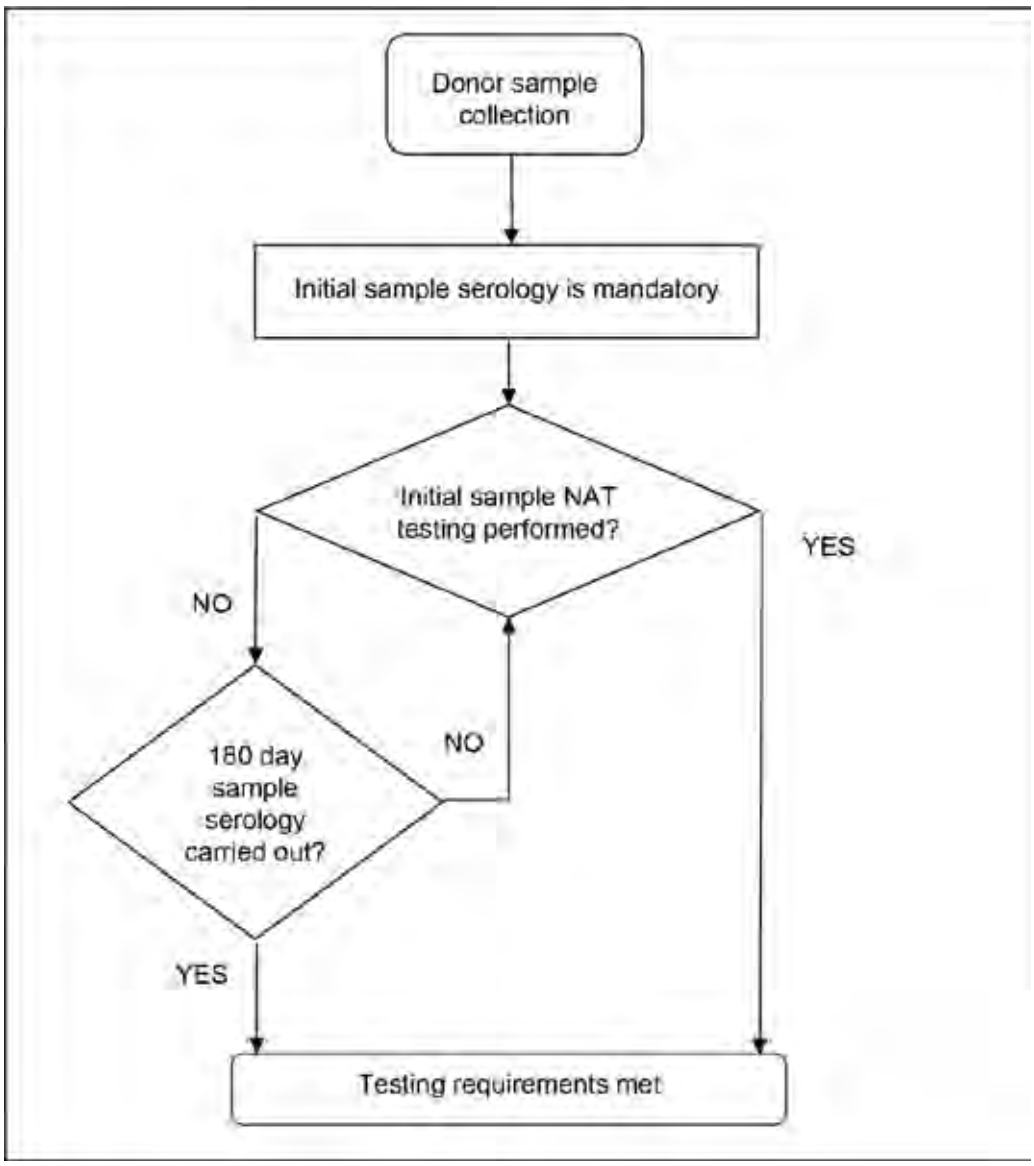
2. for blood, cells or tissues that can be stored for over 180 days, initial sample serology is mandatory, and the donor must be sampled and tested by serology more than 180 days after blood, blood component, cell or tissue collection.

If it eventuates that 180 day sample serology testing is not able to be done in scenario (2) above it may be possible to justify retrospective testing of the initial donor sample by NAT in combination with the initial sample serology. However, the validity/suitability of using donor samples that may have been held in longer-term storage prior to undertaking 'NAT testing' on the initial sample should be demonstrated under such circumstances.

Initial donor sample testing by NAT minimises the window period of infection and as such, product from a donor that has not had a sample tested by NAT must not be released until 180 day serology testing is performed.

Information on the timeframe between collection and sampling should be included in the application and may be subject to GMP inspection.

Figure 1 Flowchart detailing the requirements of subsection 11(4).



Subsection 11(4)(b) NAT testing for HIV, HCV,HBV

The requirement to perform NAT testing is to significantly shorten the window period for detection of HIV, HBV and HCV infections.

Subsection 11(6)(a) Segregation and quarantine of products for autologous use

Segregation of product requires that reactive or potentially reactive human cells or tissues be isolated physically or by other effective means from non-reactive cells or tissues to ensure cross-contamination can be avoided.

Section 12 Microbial control

This section specifies the measures that must be taken by manufacturers to minimise the risk of intrinsic and extrinsic microbial contamination of product.

Subsection 12(1) Microbial contamination minimisation strategy

This subsection prefaces this section by acknowledging that the strategies undertaken to minimise microbial contamination may depend on the specific processing and uses of the biological and includes provisions for product specific Orders.

It is acknowledged that some starting materials (e.g. skin and ocular tissue) are not sterile as they have inherent microflora that will not be eradicated by processing or manufacturing steps. The microbiological specifications for these finished products should be formulated to specify the maximum allowable level and specify the absence of 'specified microorganisms', which would render the product unsuitable for use.

Subsection 12(3) & 12(4) Transport and storage of products prior to processing

In this clause, allowance has been made for manufacturers to justify and set their own transport and storage temperature requirements prior to and after processing, unless specified in product-specific Orders. The conditions of product transport and storage should be specified to ensure maintenance of product quality including minimisation of microbial contamination.

'Plasma for fractionation' is specifically excluded from the requirements in this subsection as the transport conditions applying to such product are defined in the product specific standard applicable to these products, as defined in the European Pharmacopoeia monograph 0853 of the same name.

Subsection 12(5) Bioburden specifications

Manufacturers must have in place procedures that demonstrate criteria for acceptance and release of human blood and blood components, human tissue and human cellular therapy products based on microbial specifications, as per subsection 8(1)(c).

Approaches to the options listed as 12(5)(a), 12(5)(b) and 12(5)(c) need to be determined by the manufacturer. The pharmacopoieal default standards[1] and ISO 11737-1 *Sterilization of medical devices*[2] provide useful guidance on suitable bioburden test methods and validation to demonstrate neutralisation/inactivation of antimicrobial substances. ISO 11737-1 also describes steps to establish the recovery efficiency and correction factor(s) to be applied when testing bioburden on or within solid and semi-solid starting materials (e.g. bone, tendon, etc).

Subsection 12(5)(b) Product release bioburden specifications

Where applicable, manufacturers will be required to provide to the TGA lists of specified microorganisms (refer to the definition in Section 5 Interpretation) of clinical significance, which, if tested and found to be present, will be acceptable or require rejection of the tissue from therapeutic use. The list and justifications will be reviewed by the TGA.

Subsection 12(5)(e) Terminal sterilisation – bioburden requirements

For product that is subjected to a terminal sterilisation process, it is internationally accepted practice to require a sterility assurance level (SAL) of 10^{-6}; this is consistent with

[1] British Pharmacopoeia, European Pharmacopoeia, United States Pharmacopeia (also see TGO 77 for medicines for section refs)

[2] ISO 11737-1 – Sterilization of medical devices – Microbiological methods – Part 1: Determination of a population of microorganisms on products

the requirements for terminally sterilised therapeutic goods (e.g. injectable medicines and implantable medical devices).

Low dose irradiation is often used to reduce the bioburden, or render no microbiological contamination detectable in the finished product. However, if the product is intended to be sterile, then ISO 11137-2[3] should be used to establish the radiation sterilisation dose.

Section 13 Critical materials used in collection and manufacture

Subsection 13(1) Critical material used in manufacturing procedures

A manufacturer is not necessarily required to perform testing on critical materials to ensure they are not contaminated with or likely to introduce bacterial or other infectious agents. Selection and evaluation of a critical material could be via documents provided by the material manufacturer or of testing performed by the manufacturer, to demonstrate suitability.

Justification of the selection and evaluation of critical material should be included in submitted dossier.

Subsection 13(2)(a) Critical material that are solutions

A Sponsor will need to determine which of the options under this clause will be applicable to the critical solution in question.

If the solution is included in the Australian Register for Therapeutic Goods (ARTG), the manufacturer can cross reference the ARTG entry number and does not need to resubmit all the validation data for reassessment. The information provided should include a statement justifying that it is being used for the same purpose for which it is registered and that it meets these sterility requirements.

Subsection 13(2)(a)(ii) Critical material that are solutions that meet sterility requirements

The pharmacopoieal test for sterility is currently the test as specified in the default standards under Part 3.1 of the Act, currently the British Pharmacopoeia, the European Pharmacopoeia or the United States Pharmacopeia.

Subsection 13(2)(b) Critical materials that are antimicrobial agents

A filter integrity test should be performed on the filters used to sterilise solutions and it is necessary to verify that the sterilising filter is compatible with the antimicrobial solutions.

[3] ISO 11137-2 - Sterilization of health care products – Radiation - Part 2: Establishing the sterilization dose

Annex 1: Location of requirements in dossier

Table 1 Summary table of TGO 88 requirements and suggested dossier sections in which they can be addressed

This may be completed and submitted as Appendix 1 to the dossier.

Subsection	Summary of TGO 88 requirement	Relevant dossier section/s[4]	Summary of how requirement is met[5]	Reference documents
8(1)	General requirements	4.1. Biological starting materials		
9(1)	Donor medical and social history for living donors	4.1.1. Donor selection		
9(2)	Donor medical and social history for deceased donor	4.1.1. Donor selection		
9(3)	Evaluation of medical and social history	4.1.3. Donor evaluation and management		
9(4)	Donor deferral	4.1.3. Donor evaluation and management		
9(5)	Donor deferrals for products for autologous use	4.1.3. Donor evaluation and management		
9(6)	Donor deferral exceptions for plasma for fractionation	4.1.3. Donor evaluation and management		

[4] Suggested dossier location; actual location of information may vary depending on the nature of the product, but must be defined under this heading.

[5] Only a very brief summary is required, the entire dossier will be evaluated.

Subsection	Summary of TGO 88 requirement	Relevant dossier section/s[4]	Summary of how requirement is met[5]	Reference documents
9(7)	Donor deferral exceptions for ocular tissue	4.1.3. Donor evaluation and management		
9(8)	Reassessment of donor history for stored product	4.1.3. Donor evaluation and management 4.4.1. Release specifications		
9(9)	Vertical transmission of infectious agents	4.1.3. Donor evaluation and management		
9(10)	Deferral for live vaccine recipients	4.1.3. Donor evaluation and management		
9(11)	Live vaccine deferral exceptions	4.1.3. Donor evaluation and management		
9(12)	Donors vaccinated with killed, subunit or inactivated vaccine	4.1.3. Donor evaluation and management		
9(13)	Deferral criteria	4.1.3. Donor evaluation and management		
9(14)	Donor age	4.1.4. Donor selection 4.1.3. Donor evaluation and management		

Subsection	Summary of TGO 88 requirement	Relevant dossier section/s[4]	Summary of how requirement is met[5]	Reference documents
9(15)	Validation of donor age limits	4.1.3. Donor evaluation and management		
10(1)	Donor blood sampling	4.1.2. Donor blood sampling and testing		
10(2)	Donor blood sampling (timing)	4.1.2. Donor blood sampling and testing		
10(3)	Deceased donor blood sampling	4.1.2. Donor blood sampling and testing		
10(4)	Testing of blood samples	4.1.2. Donor blood sampling and testing		
10(5)	Blood sample testing methodology (plasma dilution)	4.1.2. Donor blood sampling and testing		
10(6)	Blood sample testing methodology/kits	4.1.2. Donor blood sampling and testing		
10(7)	Blood sample testing methodology/kits	4.1.2. Donor blood sampling and testing		

Subsection	Summary of TGO 88 requirement	Relevant dossier section/s[4]	Summary of how requirement is met[5]	Reference documents
10(8)	Evaluation of blood sample testing	4.1.3. Donor evaluation and management 4.2.4. Critical steps and intermediates		
10(9)	Blood sample collection and archiving	4.1.2. Donor blood sampling and testing		
10(10)	Blood sample retesting	4.1.2. Donor blood sampling and testing		
10(11)	Blood sample testing records	4.1.2. Donor blood sampling and testing		
11(1)	Donor evaluation	4.1.3. Donor evaluation and management		
11(2)	Donor physical assessment	4.1.2. Donor blood sampling and testing		
11(3)	Donor testing requirements	4.1.2. Donor blood sampling and testing 4.1.3. Donor evaluation and management		

Subsection	Summary of TGO 88 requirement	Relevant dossier section/s[4]	Summary of how requirement is met[5]	Reference documents
11(4)	Donor testing requirements	4.1.2. Donor blood sampling and testing 4.1.3. Donor evaluation and management		
11(5)	Donor testing requirement exceptions	4.1.2. Donor blood sampling and testing 4.1.3. Donor evaluation and management		
11(6)	Donor testing requirements for autologous use	4.1.2. Donor blood sampling and testing 4.1.3. Donor evaluation and management		
12(1)	Microbial contamination minimisation strategy	4.2.2. Description of manufacturing process and process controls 4.2.4. Critical steps and intermediates 4.2.5. Validation of the manufacturing process		
12(2)	Collection of tissues from deceased donor	4.1.4. Collection of starting material		

Subsection	Summary of TGO 88 requirement	Relevant dossier section/s[4]	Summary of how requirement is met[5]	Reference documents
12(3)	Transport and storage conditions prior to processing	4.1.4. Collection of starting material 4.7. Transportation		
12(4)	Transport and storage conditions after processing	4.5. Stability & storage 4.7. Transportation		
12(5)	Product release bioburden specifications	4.4.1. Release specifications 4.4.5. Justification of specifications		
13(1)	Critical materials (microbial contamination)	4.1.4. Collection of starting material 4.2.3. Control of material and equipment		
13(2)	Requirements for critical materials	4.1.4. Collection of starting material 4.2.3. Control of material and equipment		

References

- TGA website
  <http://www.tga.gov.au>
- TGA approach to minimising the risk of exposure to TSEs
  <http://www.tga.gov.au/industry/tse-approach.htm>
- WHO malaria information
  <http://www.who.int/malaria/en/>
- CDC malaria endemic area information
  <http://www.cdc.gov/malaria/map/>
- Council of Europe 'Guide to the preparation, use and quality assurance of blood components, 14th edition'
  <http://tots.edqm.eu/entry.htm>
- ISO (International organisation for standardization)
  <http://www.iso.org/iso/home.htm>
- Guidance for Industry: Recommendations for Obtaining a Labeling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)
  <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073972.htm>
- EMEA guidance document *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* (EMEA/410/01 rev 3, July 2011)
  <http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf>
- EMEA guidance document *Note for Guidance on Virus Validation Studies: The design, contribution and interpretation of studies validating the inactivation and removal of viruses Feb 1996*
  <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003684.pdf>
- Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation
  <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM188251.pdf>

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