ATBF Comment to

THERAPEUTIC GOODS ORDER NO. XX - Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies

February 2010

This response only includes those items wherein the ATBF wishes to submit comments at this time.

4. Interpretation

(1) For the purpose of this Order, the term "must" means that the Order is to be complied with at all times. The term "should" indicates that an activity that is strongly recommended or advised, but for which a justified effective alternative can be considered.

(2) In this Order:

***allogeneic** means material for administration to an individual that is obtained, or derived, from a genetically different individual;*

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***banked** means maintenance, under appropriate controlled conditions, in an inventory, of a finished product that has been determined suitable for supply;*

ATBF seeks clarification why the term banked appears to be confined to finished product.

***physical examination** means a clinical based inspection of a living or deceased potential donor to determine suitability of the person to be a donor and includes at minimum the relevance of any abrasion/laceration, bruise/haematoma, fracture, tattoo, piercing, scars, skin lesion, surgical incision or other distinguishing external feature that may be indicative of a behaviour, lifestyle or disease*.

ATBF suggest substituting 'identify risk factors' for "determine suitability". ATBF seeks clarification whether there is the intent for a live donor to be subjected to a full body examination? As this is not required prior to surgery such as hip replacement, it is highly unlikely that surgeons or anaesthetists will perform this task. Respect for potential donors' privacy will be a significant issue. We suggest deleting "living" or further consultation to reach a practical solution.

6. Exemptions

Human blood and blood components, human tissues and human cellular therapies exempt from the requirements of this Order:

(1) vascularised organs and associated tissue for direct organ transplant

(2) blood and blood component samples and biopsied cell or tissue samples taken for in vitro diagnosis and not for manufacture and/or reintroduction or transplant to a recipient

(3) a product in relation to which an exemption from compliance with this Order has been granted by the Secretary in accordance with section 14 and 14A of the Act

ATBF suggests the addition of “autologous tissue used in the same procedure”.

Schedule 2

The manufacturer must have the following policies in place.

(1) The manufacturer must demonstrate that steps are taken to mitigate the risk of infectious disease transmission either during collection, manufacture or via the finished product. The policy (or policies) must address the process for selection of suitable donors and include:

(a) eligibility requirements for donors who have resided/travelled outside Australia; and

(b) for manufacturers of allogeneic blood and blood components, human tissues and human cells required to be manufactured in a facility with an approved quality system, an informed risk/benefit analysis regarding donors who have resided/travelled outside Australia and at minimum, be consistent with the policy applied to donors of blood for blood components:

(i) must not be manufactured from donors who have lived in or visited England, Scotland, Wales, Northern Ireland or the Isle of Man for a cumulative period of six months or more, between 1 January 1980 and 31 December 1996 inclusive; and

(ii) must not be manufactured from donors who have received a transfusion or injection of blood or blood components while in England, Scotland, Wales, Northern Ireland or the Isle of Man from 1 January 1980 onwards.

Schedule 3

MEDICAL & SOCIAL HISTORY

This Schedule sets out the requirements relating to the collection, recording and assessment of medical and social history of prospective donors or donors of human blood and blood components, human tissues and cellular therapies.

(1) The minimum donor medical and social history criteria to be reviewed and responses documented for all donors of human blood and blood components, human tissues and human cellular therapies are set out in Table 2.

(2) Human blood and blood components, human tissues or human cells must not be collected from a living donor unless the Medical and Social History interview has been conducted by a qualified interviewer at a face-to-face interview with the donor or guardian/next-of-kin.

(a) The interview must occur as close as possible to, but at no more than 7 days prior to donation, unless (b) or (c) or (d) applies, and the history must be documented at that time.

(b) Where the interview of a donor is in relation to donation of HPC-A or HPC-M then the medical and social history of a donor must take place, or re-confirmation given if previously interviewed, within 30 days before collection of the peripheral blood or bone marrow.

(c) If a maternal donor in relation to a donation of cord blood has been interviewed earlier during pregnancy, a confirmation of the currency of the medical and social history must be provided in writing by the donor, if possible, at the time of donation, or no later than 14 days after donation.

(d) For cells and tissues, if repeat serological testing will be performed on donor blood samples collected at a minimum of 180 days after the initial sampling in accordance with Schedule 5 Item 2 (a) then the interview must occur within 90 days prior to donation and currency of the history confirmed in writing by the donor within 7 days prior to donation.

The optimal time for obtaining verbal information from a potential surgical donor is when the donor is not preoccupied, stressed or under the influence of sedatives. On the day of or immediately prior to surgery, donors are usually under duress as they are concerned with their impending procedure. Often they have been prescribed a sedative or been given premeds. The time frame of 7 days prior to donation is too restrictive and is not conducive to obtaining optimal information. Post surgery should be allowed and we suggest ‘within a month of donation’.

The ATBF seeks clarification to identify what aspect of ‘face to face” is superior to telephone interview and provide evidence to support this. ATBF seeks a consultation with TGA on this contentious topic.

(3) An interview, where possible, with the next-of-kin/guardian of a deceased donor and/or examination of the medical record to obtain and document the medical and social history of the donor must take place and be documented at the time of, or no more than 7 days prior to the donation.

ATBF queries whether ‘7 days prior’ in this instance is an accidental oversight or an inadvertent cut and paste error in that we are discussing deceased donors.

Table 2: Minimum medical and social criteria required to define a donor's risk of recent exposure to infectious disease

Donor medical and social history criteria	Period of ineligibility prior to donation for	
	Allogeneic use	**Autologous use**
(a) Tattoo or body piercing ***Body piercing should be the same as the allowance for a 'licensed practitioner'.***	6 months	Nil
(b) Acupuncture	6 months unless the acupuncture in that period was performed by a licensed practitioner using sterile non-reused needles or equipment then nil exclusion period	Nil
(c) Needle stick injury, or contact of non-intact skin or mucous membrane with blood or body fluid ***Needle stick exclusion should be the same as for a) and b)***	6 months where the injury or contact is thought to be at high risk of carrying hepatitis C, hepatitis B or HIV	Nil
(d) Inmate of a prison	12 months from date of release (when imprisoned for a consecutive period of 72 hours or more)	Nil
(e) Sex worker, or received money for sex	12 months from last contact	Nil
(f) Male to male sexual relationship	12 months from last contact	Nil
(g) A sexual relationship with a person known to □ have hepatitis C □ have HIV □ be a sex worker □ have male to male sex	12 months from last contact	Nil
(h) Ever injected any drug for a non-medical reason	Permanent	Nil
(i) A recipient of □ human derived clotting factors □ viable animal cells or tissues	Permanent	Nil
(j) Known to be infected with □ hepatitis C □ HIV □ HTLV 1/HTLV 2	Ineligible	Nil
(k) Suspected to be infected with □ hepatitis C □ HIV □ HTLV 1/HTLV 2	Ineligible until a disease free state can be established.	
(l) Known, suspected or at risk of being infected with hepatitis B	Ineligible until (i) disease resolved (donor immunised or HepBsAb≥100 IU/L) or (ii) as prescribed for the risk factors (a) to (h) above	Nil

Donor medical and social history criteria	Period of ineligibility prior to donation for	
	Allogeneic use	**Autologous use**
(m)Physical evidence of sepsis such as unexplained generalised rash/generalised petechiae	Ineligible until a disease free state can be established	Nil
(n) Active infection of the cells and tissue to be retrieved, active infection of other cells and tissues that are indicative of infection that render the target cells and tissues unsuitable for manufacture	Ineligible until a disease free state can be established	Nil
(o) Active infection of tuberculosis	Ineligible until a disease free state can be established	Nil
(p) Typhus	Ineligible until a disease free state can be established	Nil
(q) Risk of prion disease	Permanent	Nil
(r) Being a recipient of human pituitary derived growth hormone	Permanent	Nil
(s) Being a recipient of allogeneic organ(s) or cells, or deceased donor tissue allograft ***Why is a recipient of cadaveric tissue permanently deferred and there is no deferral period if the tissue donor was living? We suggest 6 months (or 12 months as for blood) exclusion for recipients of all allogeneic human tissue and cellular transplants where sourced & transplanted in Australia. Permanent could apply if the allografts were sourced o/seas.***	Permanent	Nil
(t) Being a recipient of allogeneic blood, blood components or blood products that do not meet the requirements of this Order ***ATBF seeks clarification. Does this mean that 12 months is required when the blood was sourced o/seas and no exclusion when the blood was sourced in Australia?***	12 months unless (q) or (r) apply, then permanent	Nil
(u) Being a recipient of live vaccine(s) or Hepatitis B vaccine	Ineligible for the periods specified in (5)	Nil

ATBF seeks further consultation with TGA on the contents of Table 2.

To address the possible vertical transmission of infectious agents in infant donors of less than 18 months old, or up to 6 months beyond breast feeding, whichever is greater time, the birth mother must also be evaluated for high risk behaviour according to criteria (a) to (l) of Table 2 of this Schedule and ineligibility observed as prescribed for the donor.

(5) A potential donor of allogeneic tissues or cells who received

(a) live vaccine is ineligible to donate tissues if the minimum donor exclusion period has not been exceeded as set out in Table 3.

Table 3: Ineligibility period for potential tissue donors who have received a live vaccine

Vaccines/Antisera Administered	***Vaccine Composition***	***Donor Exclusion Period***
(i) Rotavirus	*Live attenuated bacteria or viruses*	*4 weeks*
(ii) Oral Polio		
(iii) BCG		
(iv) Measles		
(v) Mumps		
(vi) Rubella		
(vii) Yellow fever		
(viii) Typhoid fever		
(ix) Cholera		
(x) Varicella		
(xi) Small pox		*8 weeks*
(xii) Antisera/Antivenins	*Sera of animal origin*	*12 weeks*
(xiii) Unlicensed vaccine	*Unknown*	*12 months*

(5) refers to donors of tissues & cells, while Table 3 refers to only potential tissue donors – is this a typo?

Schedule 4

SAMPLING, TEST KITS, TEST PROTOCOLS AND TEST MANAGEMENT

This Schedule sets out the requirements to be complied with by the manufacturer in relation to sampling, test kits to be used, test protocols to be applied and test management to be used to determine the infectious disease status of potential donors of human blood and blood components, human tissues and human cellular therapies.

(1) In order to determine the infectious disease status of persons who are potential donors of human blood and blood components, human tissues and human cellular therapies, testing must be performed on aseptically collected samples of the donor's blood for the purpose of infectious disease screening.

(2) Blood sampling of a living donor must take place,

(a) on the day of blood, cell or tissue collection; or

(b) if not possible for cells and tissue, as close as practicable prior to the time of cell or tissue collection, but no more than 7 days; or

(c) in the case of a mother of the infant donor(s) of cord blood, within 7 days (before or after) the cord blood collection; or

(d) *within 30 days before collection of peripheral blood or bone marrow for manufacture of HPC-A or HPC-M*

Allowance should be made for donors who will be retested at 180 days post donation. For these, we suggest allowing up to one month after donation.
Clarify the requirements for 'autologous'. Autologous should be exempt for 2b.

(3) Blood sampling of a deceased donor must take place prior to cell or tissue collection and no later than 24 hours after death, if a pre-mortem blood sample is not available.

ATBF suggests that this clause needs to be reworded as it suggests that a pre-mortem blood sample has to be used if it is available even though the post-mortem sample is suitable. Where the pre-mortem sample is not readily available, a delay in testing will negatively impact on the whole process. We suggest the following wording: "Blood sampling of a deceased donor must take place prior to cell or tissue collection and no later than 24 hours after death. A pre-mortem blood sample collected up to seven (7) days prior to donation may be used if available and suitable.

(4) For manufacture of blood, blood components, tissue and cellular therapies, testing of the samples for infectious diseases must normally be performed

(a) as soon as practicable; or

(b) within 30 days before collection of peripheral blood or bone marrow for therapeutic goods that are HPC-A and HPC-M, respectively.

(5) The testing of blood samples from donors must take into account any factors which may cause plasma dilution sufficient to alter serology test results. When a potential donor has lost blood and has recently received donated blood, blood components, colloids or crystalloids, blood testing may not be valid due to dilution of the sample. Where a pre-transfusion sample is unavailable for infectious disease testing, an algorithm must be applied to assess the degree of dilution. A plasma dilution factor must be less than 50%, i.e. must not exceed the donor's own plasma volume.

The test kits/methodologies used for the mandatory tests for screening must

(a) be current technology; and

ATBF submits that at times "current" technology is not the most appropriate for the circumstance (e.g. NAAT vs 180 day retesting). We suggest substituting "appropriate technology /methodology".

(b) have regulatory approval for the intended use; and

(c) be used in accordance with the approved methodology (i.e. in accordance with the test kit instructions); and

(d) be validated for the purpose for which it is to be used. In the case of any changes to test methodology, these must also be formally validated and documented.

(7) The test kits used in evaluation of donor samples must be documented.

(8) Screening and confirmatory microbiological and virological tests must be performed in laboratories using appropriately validated testing techniques as regulatory requirements specify.

(9) Samples of donor serum/plasma must be archived under optimal conditions to ensure sample availability for retesting or additional testing up to, at minimum, the time of transfusion or implantation of human blood and blood components, human tissues or human cellular therapies.

(10) *Dedicated samples of the serum from deceased or living donors taken at time of donation, and also the samples taken from live donors at 180 days post-donation, must be archived at or below minus 25°C unless the conditions of archive are validated at a different temperature (or as recommended by the test kit manufacturers) for the period from sample collection to a minimum of 2 years after the expiry date of the human blood and blood components, human tissues or human cellular therapies*.

ATBF queries why the samples for living donors that have been collected at the time of donation be archived when samples are collected at 180 days and these are archived? We suggest only requiring the 180 days samples to be archived for the retested donors.

'Minimum of 2 years after the expiry date' is not the same as 'the time of transfusion or implantation…' as stated in (9). As it is acknowledged that "Minimum of 2 years after the expiry date" will cover "the time of transfusion or implantation" we suggest "Minimum of 2 years after the expiry date" be applied in (9).

(11) Where screening protocols change during the life of a product in storage, where possible and practicable the donor's archived serum/plasma must be retested with the new screening test protocol prior to release of human blood and blood components, human tissue or human cellular therapy products.

ATBF seeks clarification about future interpretations of what is possible and practicable, We request either definition of "possible and practicable" and / or provide for undertaking a risk assessment to determine retesting requirements.

(12) Documentation of the tests performed, test modifications, analyses and any anomalies required to be appended to the donor record in addition to the test results.

(13) *Results of all tests, including indeterminate or initial reactive test results, and examinations performed must be documented in the donor record.*

ATBF seeks clarification as to the rationale and need to include indeterminate or initial reactive results if the repeat test is non-reactive in the donor record (given the 'approved' screening pack inserts themselves state to report these as negative)?

Schedule 5

DONOR TESTING AND EXAMINATION

This Schedule sets out the requirements in relation to donor testing and examination.

(1) Each donor of human blood and blood components, human tissues or human cellular therapies must be tested and examined for evidence of infectious diseases in accordance with the relevant and applicable donor groups. Assessment of donor blood samples and the physical examination of the donor are key determinants of donor acceptability or rejection. Donors of human blood and blood components, human tissues and human cellular therapies must be evaluated as follows:

(a) The donor testing must include, at minimum, serological tests and, unless justified otherwise (e.g. donor sampling and testing at ≥180 days after the initial blood sample is taken, or time restrictions due to tissue lability), tests using Nucleic Acid Amplification Technology (NAAT[1]), where available, for the infectious diseases/infectious disease markers as indicated in Table 4 of this Schedule.

ATBF seeks clarification whether or not NAAT is required in addition to 180 days retest.

(b) To address the possible vertical transmission of infectious agents in infant donors of less than 18 months old, or up to 6 months beyond breast feeding, whichever is the greater time,

(i) the birth mother must also be screened and tested in accordance with Schedules 4 and 5(1)(a);

(ii) for cord blood, each cord unit must be tested according to Table 4 prior to release. Units for allogeneic transfusion must be negative when tested..

(c) A physical examination must be conducted by a competent person to ascertain the suitability of a donor to donate cells or tissues and must take place,

(i) on the day of blood, cell or tissue collection; or

(ii) if not possible for cells and tissue, as close as practicable prior to the time of cell or tissue collection, i.e. generally within 5 days and no more than 7 days; or

(iii) *for a deceased donor, prior to cell or tissue collection and no later than 24 hours after death;*

Please refer to our comments regarding "ascertain suitability" and 'examination of a living donor' under "physical examination" at Schedule 3 (2). 'Physical examination' of living donors is not appropriate.

(d) The cells and tissues of a deceased donor whose cause of death is unknown must be deemed unacceptable, unless autopsy provides sufficient information to conclude that death has not been caused by a transmissible disease or any other condition that would be a contraindication or preclude transplantation of the cells or tissue from that donor.

(2) Where cells and tissues can be stored for long periods without impairing fitness for use, repeat sampling and serological or NAAT testing of the living donor

[1] NAAT and serological tests used for screening blood from a deceased donor blood must have been validated for post mortem samples.

(a) for HIV, HBV and HCV must be performed at a minimum of 180 days after collection of the donation sample, to provide assurance that the initial sample was not collected during the window period for infection.

(b) and the donor of a rare cell or tissue type is not available for the repeat 180 day sampling, the initial donor sample must be tested by NAAT for HIV, HCV and HBV (when available).

ATBF seeks clarification on these points:

- Is NAAT for living donors required in addition to 180 days retest?
- Can NAAT be allowed in place of 180 days retest?
- Should syphilis be included here?

ATBF suggest that as HTLV is extremely rare, the probability of finding a positive donor is highly unlikely. (2 per 6,500 donors since 1999 at PBTB). Hence HTLV testing at the 180 days retest should be permitted as an alternative to testing at time of donation provided the donation remains unopened until the 180 days blood test results are received.

(3) In cases where a human blood and blood component, human tissue or human cellular therapy is manufactured from a donor with repeatedly reactive mandatory screening tests, with the intended purpose of reintroduction into that donor

(a) segregation and quarantine must be applied to that human blood and blood component, human tissue or human cellular therapy and cross-contamination is to be avoided; and

(b) records must be available to demonstrate the rationale for the use of the product. Authority for the release of this product must also be documented.

(4) Examination for microbiological contamination of donor cell or tissue specimens must be performed using a validated method.

(5) For blood and blood components, human tissues and human cellular therapies required to be manufactured in a facility with an approved quality system, the bioburden of the cell or tissue specimens must be determined and the results recorded. Specifications for the human blood and blood components, human tissues or human cellular therapy must be in accordance with

ATBF suggest the replacement of “the bioburden of the…” with “microbiological assessment of the” …

(a) those set in the respective product specific Orders, or

(b) those set based on established and clinically acceptable numbers and types of organisms for the indication of use and should include

(i) a limit for Total Viable Count (aerobic and anaerobic microorganisms); and
(ii) absence of specified microorganisms of clinical significance.

Table 4: Donor testing requirements

ID testing			Deceased donors[a]	Cornea only donors	Living donors[b]										HPC-C units Release tests	
					Allogeneic use[b]						Autologous use					
					Blood / components	Plasma only	HPC-A HPC-M	HPC-C	Domino donor	Other	Blood	HPC-A HPC-M	HPC-C[b]	Other	Allogeneic	Autologous
Serology	Initial sample	anti HIV-1	√ X	√ X	√ X	√ X	√ X	√ X	√ X	√ X	√	√	√	√	√ X	√
		anti HIV-2	√ X	√ X	√ X	√ X	√ X	√ X	√ X	√ X	√	√	√	√	√ X	√
		anti HCV	√ X	√ X	√ X	√ X	√ X	√ X	√ X	√ X	√	√	√	√	√ X	√
		HBsAg	√ X		√ X		√ X	√ X[c]	√ X	√ X	√	√	√ [c]	√	√ X	√
		HBcAb [2]	√ X		√ X		√ X	√ X	√ X	√ X	√	√	√	√	√ X	√
		HTLV1/2 (antibodies)	√ X		√ X		√ X	√ X[d]	√ X	√ X	√	√	√ [d]	√	√ X	√
		syphilis [3]	√ X		√ X	√ X	√ X		√ X	√ X[e]	√	√		√		
NAAT	Initial sample	HIV	√ X		√ X	√ X	√ X		√ X	√ X[e]	√	√		√		
		HCV	√ X		√ X	√ X	√ X		√ X	√ X[e]	√	√		√		
		HBV (when approved)						√ X		√ X[e]			√			
Serology/ NAAT[c]	18 0 sample	anti HIV-1						√ X		√ X[e]			√			
		anti HIV-2						√ X		√ X[e]			√			
		anti HCV						√ X		√ X[e]			√			
		HBsAg														
		HBcAb														

√ X indicates that the test **must** be performed and the test **must** demonstrate that the samples tested are non-reactive

√ indicates that the test **must** be performed and if the test demonstrates that the samples tested are reactive then Schedule 5(3) applies [a] includes testing to be performed on blood samples of deceased donors for the donation of any tissue other than cornea

[b] additional testing provisions as specified in Schedule 5(2) apply to some living donors of cells and tissues to be used for allogeneic use and to the maternal donor of cord blood [c] for a HPC-C unit, the maternal sample may be acceptable if reactive for HBcAb provided it satisfies the criteria given in [2] or if hepatitis B antigen negative

when tested by DNA
testing (NAAT)

d if a maternal sample is syphilis screen positive but tests negative using a specific confirmatory test the sample may be considered acceptable.

e (2) of this Schedule applies

[2] A HBcAb reactive sample is acceptable only if HBsAb when tested is ≥100 IU/L, or a specified recipient is known to be immune to HBV.

[3] Non-specific (reaginic) syphilis tests are prone to false positive results. Therefore specific syphilis testing must be conducted on tissue donors, where it is required.

Schedule 6

SUBSTANCES USED IN PRODUCTION

This Schedule sets out the requirements in relation to the selection and evaluation of any critical materials employed during the manufacture (collection, processing, storage or transport) of human blood and blood components, human tissues or human cellular therapies.

(1) Critical materials employed in the processing of human blood, blood components, human tissues or human cellular therapies must be selected and evaluated to ensure they are not contaminated with or likely to introduce pathogenic bacteria or other infectious agents to the human blood, blood components, human tissues or cellular therapy.

(2) Where blood, cells and tissues are required to be manufactured in a facility with an approved quality system, critical materials used in manufacture that are

(a) solutions, other than the disinfectant/antiseptic [4] solutions used in a validated tissue cleaning process, which contact the human cells or tissue during collection, processing, storage or transport must be

(i) manufactured under an approved quality management system and be supplied as a sterile solution; or

(ii) tested for and satisfy sterility requirements in accordance with an approved pharmacopoeial test for sterility; or

(iii) if required by the Act, approved for an equivalent purpose and entered on the ARTG.

(b) material, other than the starting materials of blood, cells or tissue, containing any components of human or animal origin, must have been sourced, tested (if methodology is available) and assessed as presenting a minimal risk of transmitting infectious disease agents [refer TGA[5] and EMEA[6] Guidelines]. If the product is not required to be on the ARTG, the recorded information must include at minimum[7]:

(i) Screening tests performed;

(ii) QC specifications, e.g. criteria and limits for the tests performed;

(iii) *Storage conditions*

[4] Antibiotic/antimicrobial solutions should be sterile. If they are not supplied sterile by the solution manufacturer, they should be sterilised by filtration through a 0.22µm filter prior to use and aseptically dispensed at time of use to prevent further contamination of the tissue.

[5] TGA approach to minimising the risk of exposure to Transmissible Spongiform Encephalopathies (TSEs) through medicines and medical devices < http://www.tga.gov.au/docs/html/tsepolicy.htm>

[6] EMEA Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 rev 2, October 2003 (pdf,181kb) < http://www.emea.europa.eu/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf>

EMEA CPMP) 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.emea.europa.eu/pdfs/human/bwp/026895en.pdf >

[7] If this information is not available from the manufacturer of the material, the material will need to be assessed by the manufacturer of the human blood and blood component, human tissue or cellular therapy.