2 February 2011

Administration Officer
Biological Science Section
Office of Scientific Evaluation
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Dear Sir/Madam

Standards Consultation (*TGO No. XX – Standards for minimizing infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products*) –feedback

Thank-you once again for providing the opportunity to provide feedback on the aforementioned proposed Therapeutic Goods Order (TGO) currently under consultation.

[redacted] welcomes the consideration of some of our earlier expressed concerns by TGA in the latest version of the proposed TGO. [redacted] still believes however, that the proposed Order does not give due consideration to some of the internationally accepted, rigorous safety procedures relating to Plasma for Fractionation provided by the Plasma Master File (PMF) system, and additionally imposes requirements in excess of the Pharmacopoeial Monograph for Plasma for Fractionation. This imposes an unnecessary and unacceptable regulatory burden upon [redacted] and its global customers, which makes the operation of our plasma fractionation business and commercial export business in Australia difficult and indeed impossible for several overseas markets. The Order as proposed is believed to be an unnecessary restraint on trade. [redacted] has provided additional comments and suggestions annotated in the attached draft TGO for consideration by the TGA.

[redacted] would appreciate further explanation of the Sections 14 & 14A exemption processes in relation to Plasma Master Files, particularly in relation to *export only* products, since this process would be the main option for full compliance with this Order for our international customers and markets.

Australian Government

Department of Health and Ageing

THERAPEUTIC GOODS ACT 1989
Section 10

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 therapy products*

I, Rohan Hammett, delegate of the Minister for Health and Ageing for the purposes of section 10 of the *Therapeutic Goods Act 1989* and acting under that section, having consulted with the Therapeutic Goods Committee in accordance with subsection 10(4) of that Act, HEREBY:

(a) DETERMINE that the matters specified in this Order shall constitute a standard for the following:

(i) donor selection;

(ii) donor testing; and

(iii) blood, blood component, cells and tissue collection and manufacture

to minimise infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products.

Dated this ….. day of ……. 2011

Rohan Hammett
Delegate of the Minister for Health and Ageing

(iv) PART 1 - INTRODUCTION

1. Name of Order

This Order may be cited as *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 therapy products* .

2. Commencement

This Order commences on the day after the day it is registered on the Federal Register of Legislative Instruments.

3. Purpose of this Order

This Order sets out particular requirements for minimising the risk of transmission of infectious disease via human blood and blood components, human tissues and human cellular therapy products. It specifies the minimum general requirements as related to infectious agents for donor selection, donor testing, blood, cells and tissue collection and manufacture for all human blood and blood components, human tissues and human cellular therapy products.

For regulatory purposes it will be necessary to reference current product specific Orders made for the purposes of section 10 of the Act, where they apply, which establish additional criteria for collection, manufacture and release of a particular human blood or blood component, human tissue or human cellular therapy products.

4. Interpretation

(1) For the purpose of this Order, the presence of the term "must" in relation to a particular requirement in a provision set out in this Order means that the requirement is to be complied with at all times. The presence of the term "should" in relation to a particular requirement set out in this Order indicates that the requirement is strongly recommended or advised, but for which a justified effective alternative can be considered to comply with such requirement.

(2) In this Order:

allogeneic use means the use of blood, blood components, tissues and cellular therapy products that are removed from one person and applied to another person.

antimicrobial means the ability of a substance to kill or inhibit growth of microorganisms.

aseptic technique means the measures used to prevent contamination by microorganisms.

asystole means the reference time for cardiac death. A documented pronounced time of death is used as asystole when life-saving procedures have been attempted and there were signs of, or documentation of, recent life (e.g. agonal respirations, pulseless electrical activity). If death was not witnessed, 'asystole' must be determined by the last time known alive. Asystole will be 'cross clamp time' if the tissue donor was also a solid organ donor.

autologous use means the use of blood, blood components, tissues and cellular therapy products that are removed from and applied to the same person.

bioburden has the same meaning as in "bioburden" in subsection 3(1) of the *Therapeutic Goods Act 1989*, as amended from time to time.

blood means whole blood collected from a single human donor and processed either for transfusion or further manufacturing.

blood components means components of blood (red cells, white cells, platelets, plasma for infusion and plasma for fractionation) that can be prepared by centrifugation, filtration and freezing, but not including haematopoietic progenitor cells.

cell(s) means individual cells or a collection of cells when not bound by any form of connective tissue.

collection means the process of removing human blood, blood components , cells, or tissue from a donor.

critical material means all components, materials or supplies which could have a direct impact on the quality, safety and function of the end product.

cryopreserved means suspended in a validated medium containing a suitable cryoprotectant and cooled according to a validated method that allows maintenance for long periods.

domino donor means a person who by receiving an organ transplant donates the removed organ or tissue for allogeneic use.

donor means every source, whether living or deceased, of blood, blood components, cells or tissues

extrinsic microbial contamination means contamination of the product caused by compromised processing**.**

haematopoietic progenitor cells means cells that are primitive multipotent cells capable of self-renewal as well as differentiation and maturation into all haematopoietic lineages.

HBsAg means Hepatitis B surface antigen.

HBV means Hepatitis B virus.

HCV means Hepatitis C virus.

HIV means Human Immunodeficiency Virus.

HPC means haematopoietic progenitor cells.

HPC-A means haematopoietic progenitor cells-apheresis.

HPC-C means haematopoietic progenitor cells-cord.

HPC-M means haematopoietic progenitor cells-marrow.

HTLV-1 means Human T-Lymphotropic Viruses type 1.

HTLV-2 means Human T-Lymphotropic Viruses type 2.

intrinsic microbial contamination means contamination of the product with microorganisms already present in the starting material;

knowledgeable historian means a person knowledgeable about the donor's medical and social history, if the donor is deceased or unable to participate in an interview. A knowledgeable historian may be a person, or persons, able to provide relevant information and may be the donor's next of kin; the nearest available relative; a member of the donor's household; a person with a relationship with the donor (for example, carer, friend, partner); or the donor's treating physician.

manufacture has the same meaning as in 'manufacture' in subsection 3(1) of the *Therapeutic Goods Act 1989*, as amended from time to time.

microbial means microorganisms including, but not limited to, bacteria, fungi, Mycoplasma and Rickettsia, but does not include viruses or prions.

NAT means Nucleic acid Amplification Technique.

physical assessment means a clinical inspection of a living or deceased potential donor to determine suitability of the person to be a donor and may include, but is not limited to, 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 or lifestyle, or suggestive of any risk factor for a relevant communicable disease.

plasma dilution means a decrease in the concentration of the donor's plasma proteins and circulating antigens or antibodies resulting from the transfusion of blood or blood components and/or infusion of fluids, e.g. colloid(s) and/or crystalloid(s).

pre-mortem blood sample means a blood sample collected prior to cardiac death of a person.

prion disease, risk of means having been exposed to the putative causative agent(s) of any one of the family of pathogenic transmissible spongiform encephalopathies through the following means:

(a) genetic (familial), or
(b) environmental, which includes 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 1st January 1980 and 31st December 1996 inclusive, or
(c) iatrogenic, which includes 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 1st January 1980 onwards

Comment [m1]: There is still inconsistency with the definition of 'UK' against EU recommendations for residency.

Comment [m2]: Comment as above.

processing means any operation involved in preparation, manipulation, preservation for storage and packaging of a blood, blood component, tissue or cell therapy product.

QC means quality control.

quarantine means the status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.

recipient means a person who receives blood, blood components, cells or tissues by infusion or implantation.

Register has the same meaning as "Register" under subsection 3(1) of the *Therapeutic Goods Act 1989* as amended from time to time.

> ***Note "Register"*** under the Act means the Australian Register of Therapeutic Goods maintained under section 9A.

specified microorganism means a microorganism which, if isolated from the tissue, necessitates discard of the tissue.

storage means the process of maintaining a substance, material or product under appropriate controlled conditions.

tissue means all constituent parts of the body formed by cells.

transport means transfer within or between premises of a substance, material or product under appropriate controlled conditions.

trained interviewer means a person who is trained in interviewing skills and is an employee of, or has a contractual arrangement with, a manufacturer.

trained assessor means a person who is trained in physical assessment and is an employee of, or has a contractual arrangement with, a manufacturer.

TSE means transmissible spongiform encephalopathy.

virological means pertaining to viruses.

5. Application of this Order

(1) Subject to section 6, the requirements of this Order apply to human blood and blood components, human tissues and human cellular therapy products that are collected from

(a) a living human donor and intended for autologous use; or

(b) a living human donor and intended for allogeneic use; or

(c) a deceased human donor and intended for allogeneic use; or

~~(e)~~(d) a living human donor and intended for further manufacture.

Comment [m3]: This implies intended for transfusion ie. removed from one person and applied to another person?

6. Exemptions

The requirements of this Order do not apply to the following:

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

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

(3) human blood, blood components and haematopoietic progenitor cells that are:

(a) collected by a medical practitioner, registered under a law of a State or Territory, or a person under the professional supervision of such a practitioner, in the course of medical treatment and for the purposes of diagnosis of, and testing for, a medical condition; or

(b) manufactured by a medical practitioner, registered under a law of a State or Territory, or a person under the professional supervision of such a practitioner, for therapeutic application to a patient under the practitioner's care; or

(c) manufactured by a blood donation centre for a medical practitioner who is registered under a law of a State or Territory, for therapeutic application to a particular patient under the practitioner's care

(4) 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.

Comment [m4]: The Process for applying for a S14 exemption needs further explanation and definition for Plasma Master Files, particularly for 'export only' products.

(v) PART 2 – GENERAL REQUIREMENTS

7. General requirements for human blood and blood components, human tissues and human cellular therapy products

(1) The manufacturer must have procedures in place that demonstrate:

(a) steps taken to mitigate the risk of infectious disease transmission during collection and manufacture; and

(b) processes for notifying persons/organisations of a donor test result that is positive or reactive to an infectious disease; and

(c) criteria for acceptance and release of human blood and blood components, human tissue and human cellular therapy products based on microbial specifications.

(vi) PART 3 – SPECIFIC REQUIREMENTS

8. Requirements in relation to the medical and social history of prospective donors

(1) Blood, blood components, cells or tissues must be collected from a living donor with whom a Medical and Social History interview has been conducted and recorded. The interview that is required must be in accordance with the following:

(a) The interview must be conducted by a trained interviewer and should be at a face-to-face interview with the donor or guardian/next-of- kin.

(b) The interview must occur no more than 7 days prior to or 30 days after collection, and must occur prior to release of product from quarantine, unless otherwise specified in product-specific Orders under section 10 of the Act.

(2) An interview, where possible, with the next-of-kin/guardian or other knowledgeable historian of a deceased donor and/or examination of the medical documentation to obtain and record the medical and social history of the donor must take place and be recorded at the time of, or no more than 7 days prior to or following collection.

(3) Donor medical and social history criteria as set out in column 1 of Table 1 must be reviewed and responses at interview evaluated using these criteria.

(4) A donor identified in column 1 of Table 1 is subject to periods of ineligibility prior to donation are as set out in column 2 of Table 1.

(a) For donors of blood, blood components, cells or tissues for autologous use, periods of ineligibility are not applicable.

Table 1: Minimum medical and social criteria required to determine donor risk of exposure to infectious disease and ineligibility periods

Donor medical and social history criteria	Period of ineligibility prior to donation *(donors of products for allogeneic use only)*
(a) A donor known to be infected with (i) HCV (ii) HIV (iii) HTLV-1/HTLV-2	Permanently ineligible
(b) A donor suspected to be infected with (i) HCV (ii) HIV (iii) HTLV-1/HTLV-2	Ineligible until an uninfected state can be established.
(c) A donor known to be, or suspected of being, infected with HBV	Permanently ineligible except HBsAg negative persons who are demonstrated to be immune
(d) A donor who has ever injected any drug for a non-medical reason	Permanently ineligible
(e) A recipient of (i) human derived clotting factors that are not in accordance with the requirements of this Order (ii) viable animal cells or tissues	Permanently ineligible
(f) A donor with a risk of prion disease	Permanently ineligible
(g) A recipient of human pituitary derived growth hormone	Permanently ineligible
(h) A deceased donor who has been a recipient of allogeneic organ(s), cells, or tissue that are not in accordance with the requirements of this Order	Permanently ineligible
(i) A recipient of allogeneic blood, blood components or blood products, organs, cells or tissues that are not in accordance with the requirements of this Order	Ineligible for 12 months unless (f) or (g) apply, then permanently ineligible
(j) A donor whose sexual practices put them at increased risk of acquiring infectious diseases that can be transmitted by blood, cells or tissues	Ineligible for 12 months from last contact
(k) An inmate of a prison	Ineligible for 12 months from date of release (when imprisoned for a consecutive period of 72 hours or more)
(l) A donor with an unexplained fever or infectious illness	Ineligible for at least 2 weeks following the date of full recovery
(m) A donor who has lived in a malarial area within the first five years of life	Ineligible for 3 years from last visit to any endemic area provided the person remains free of symptoms; this may be reduced to 4 months if an immunologic or molecular genomic test is negative at donation

Donor medical and social history criteria	Period of ineligibility prior to donation *(donors of products for allogeneic use only)*
(n) A donor with a history of malaria	Ineligible for 3 years from last visit to any endemic area provided the person remains free of symptoms; this may be reduced to 4 months if an immunologic or molecular genomic test is negative at donation
(o) An asymptomatic visitor to endemic malarial areas	Ineligible for 6 months after leaving the endemic area unless an immunologic or molecular genomic test is negative
(p) A donor with a history of undiagnosed febrile illness during or within 6 months of a visit to a malarial endemic area	Ineligible for 3 years following resolution of symptoms; this may be reduced to 4 months if an immunologic or molecular genomic test is negative.
(q) A donor with exposure to risk of acquiring a blood borne transmissible infection (i) Mucosal splash with blood (ii) Needle stick injury (iii) Tattoo (iv) Body piercing (v) Acupuncture unless performed using sterile single use needles	Ineligible for 6 months from the time of exposure, or for 4 months provided NAT test for HCV is negative.
(r) A donor with active infection of the cells or tissue to be collected, or active infection of other cells or tissues that are indicative of infection that render the target cells or tissues unsuitable for manufacture	Ineligible until a disease free state can be established
(s) A donor with exposure to particular epidemiological situations (e.g. disease outbreaks)	Deferral consistent with the epidemiological situation and these deferrals should be notified to the Head of the Office of Scientific Evaluation of the Therapeutic Goods Administration.

(5) The testing and deferral period requirements of Table 1 (a)(iii), (b)(iii), (h), (m), (n), (o), (p), ~~(q)~~ are not required to be met when the donation is to be used exclusively for plasma for fractionation.

(6) 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 (e), (j), (k), (o) and (r) in Table 1, and ineligibility periods must be observed as prescribed for the donor.

(7) In addition to the requirements in Clause (4), a potential donor of products for allogeneic use who was vaccinated with a live vaccine is ineligible to donate if the minimum donor exclusion period has not been exceeded as set out in Table 2.

Table 2: Ineligibility period for allogeneic use for potential donors who have received a live vaccine

	Vaccine Composition	Period of donor ineligibility prior to donation
(i)	Live attenuated bacteria or viruses, except smallpox	4 weeks
(ii)	Smallpox	8 weeks
(iii)	Sera of animal origin	12 weeks
(iv)	Unknown	12 months

(8) The requirements relating to ineligibility in Table 2 do not apply when the donation is used exclusively for the purpose of plasma for fractionation.

(9) A potential donor of products for allogeneic use who was vaccinated with any of the following vaccines, and is not covered by any of the criteria in column 1 of Table 2, is not required to comply with specified deferrals provided the donor is not showing signs or symptoms of illness or disease:

(a) Cholera and typhoid vaccines with killed bacteria

(b) Capsular polysaccharide typhoid fever vaccine

(c) Vaccines with inactivated viruses

(d) Toxoids

(e) Diphtheria and tetanus

(f) Hepatitis A and Hepatitis B 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

(g) Rabies, tick-borne encephalitis (where exposure has occurred a one year deferral post exposure is required)

(h) Meningococcal vaccine

(i) Subunit vaccines e.g. cervical cancer vaccine

(10) A product must not be manufactured from a donor who is known to have a disease or condition, including those that are a consequence of donor treatment (for example, tissues exposed to irradiation), that may compromise the quality, safety or efficacy of the blood, blood component, cells or tissue for the intended therapeutic purpose, unless

(a) acceptance and deferral criteria for donors with specified diseases or conditions are based on data validated by the manufacturer, or documented evidence obtained from scientific literature review, which supports quality, safety, and efficacy of the product for the intended therapeutic purpose, or;

(b) where the condition has not been specifically identified in the donor acceptance and deferral criteria, individual donors may be subject to review and subsequent acceptance by the manufacturer's medical officer. The rationale for such acceptance must be recorded.

(11) A product must not be manufactured from blood, blood components, cells or tissues collected from a donor if the age of the donor compromises the safety and efficacy of the blood, blood components, cells or tissues.

(a) Each manufacturer must have a documented guideline regarding upper and lower age limits for donation.

(b) The age range of donors from whom specific cells and tissues can be collected must be supported by validated data or documented evidence from the scientific literature which justify appropriateness for the intended therapeutic purpose.

9. Requirements in relation to donor blood sampling, test kits, test protocols and test management

(1) To determine the infectious disease status of persons who are potential donors of human blood and blood components, human tissues and human cellular therapy products, 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) no more than 7 days prior to or 7 days after collection of blood, blood components, cells or tissue; or

(b) as set in the respective product specific Order under section 10 of the Act.

(3) Blood sampling for testing of a deceased donor must take place no later than 24 hours after asystole. A pre-mortem blood sample taken up to 7 days prior to collection of the product may be used if available and suitable.

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

(a) as soon as practicable; or

(b) as set in the respective product specific Order under section 10 of the Act, and

(c) the results evaluated prior to release of the product from quarantine.

(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. Where a pre-transfusion sample is unavailable for infectious disease testing, an algorithm must be utilised that evaluates the volumes administered in the 48 hours prior to collecting the blood specimen from the donor to ensure that there has not been plasma dilution sufficient to affect test results.

(6) The test kits/methodologies used for the mandatory screening and confirmatory microbial and virological tests must:

(a) be the most appropriate technology/ methodology for the sample being tested; and

(b) be approved by the relevant regulatory authority in the country in which the testing is performed, or, performed in a facility approved by the same authority to perform such testing.

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

(8) Dedicated samples of the serum or plasma from deceased or living donors taken at time of collection, and/or the samples taken from living donors at 180 days post-collection, must be archived at or below minus 25°C (unless the conditions of archive are validated by the manufacturer at a different temperature or as recommended by the test kit manufacturers) to ensure sample availability for retesting or additional testing up to, at

minimum, 2 years after the expiry date of products or as set out in product specific Orders for the purposes of section 10 of the Act.

Comment [m5]: What is the definition of 'products' in this instance? If this is defined as finished product eg. Albumin, this period of archival could imply up to 10 years! Would this be applicable to 'export only' plasma who have their own local regulatory requirements and may not have the required resources to accommodate this Australian requirement?

(9) Where screening protocols change during the life of a product in storage, the donor's archived sample must be retested with the new screening test protocol prior to release of the product, as determined by the manufacturer based on risk, and in consultation with the regulator.

(10) Records on individual donors of the tests performed, test modifications, test results, analyses and any anomalies must be maintained.

10. Requirements in relation to donor physical assessment and testing

(1) Each donor of human blood and blood components, human tissues or human cellular therapy products must be assessed and tested for evidence of infectious diseases in accordance with the relevant and applicable donor groups. Assessment of donor blood samples and the physical assessment of the donor are key determinants of donor acceptability, temporary deferral or rejection. Donors of human blood and blood components, human tissues and human cellular therapy products must be evaluated.

(2) A physical assessment of the donor must be conducted by a trained assessor, and must take place

(a) for a living donor at the time of donation, unless specified in the product specific Order;

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

(c) 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.

(3) All donors must be tested in accordance with the requirements set out in Table 3:

(a) ✓ in Table 3 indicates that the test must be performed

i. For all donors except autologous donors, the test must demonstrate that the samples tested are non-reactive

ii. For autologous donors, test must be performed and if the test demonstrates that the samples tested are reactive then Section 10 (6) applies

(b) For HPC-C, testing requirements of Table 3 apply only to the birth mother and do not apply to the donor infant

(c) Requirement in column 2 for deceased donors includes testing to be performed on blood samples of deceased donors for the donation of any tissue other than cornea

(4) All donors must be tested in accordance with and must comply with the following requirements:

(a) all donors must be tested by serology at the time of collection, and

(b) NAT testing for HIV, HCV and HBV must be performed at the time of collection to exclude a window period infection; or

(c) where products can be stored for more than 180 days without impairing fitness of product for use the donor must be repeat sampled after 180 days post collection and tested by serology for HIV, HCV and HBV to exclude a window period infection, unless NAT testing has been performed at the time of collection

(d) 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, the birth mother must also be screened and tested in accordance with Section 9 and Section 10 (4)(a) to (c).

(5) The requirement to test for HBV by NAT in Section 10 (4)(b) or (4)(c) does not apply when the donation is used exclusively for the purpose of plasma for fractionation

(6) In cases where human blood or blood components, human tissue or human cellular therapy products are manufactured for autologous use from a donor with repeatedly reactive mandatory screening tests:

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

(b) if requested, records must be made available to the Head of the Office of Scientific Evaluation of the TGA to demonstrate the rationale for the use of the product.

Table 3: Donor testing requirements

ID testing		Deceased donors	Cornea only donors	Living donors									
				Allogeneic use						Autologous use			
				Blood / components	Plasma for fractionation	HPC-A HPC-M	HPC-C	Domino donor	Other	Blood / components	HPC-A HPC-M	HPC-C	Other
Serology test Initial sample	anti HIV-1 anti HIV-2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	anti HCV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	HBsAg	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	HTLV-1/2 (antibodies)	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓
	syphilis	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓
AND													
NAT Initial sample	HIV	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	HCV	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	HBV	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓
OR	**OR**			**OR**		**OR**	**OR**	**OR**	**OR**	**OR**	**OR**	**OR**	**OR**
Serology ≥180 day sample	anti HIV-1 anti HIV-2			✓		✓	✓	✓	✓	✓	✓	✓	✓
	anti HCV			✓		✓	✓	✓	✓	✓	✓	✓	✓
	HBsAg			✓		✓	✓	✓	✓	✓	✓	✓	✓

11. Requirements in relation to microbial control

(1) A strategy for the minimisation of the intrinsic and extrinsic microbial contamination in a product must be established based on a risk assessment considering the nature and intended use of the product.

(2) Human cells and tissues from a deceased donor must be collected

(a) as soon as possible after asystole and take place within 24 hours of asystole provided the body has been refrigerated at 2°C to 8°C within 12 hours of asystole; or

(b) if the body has not been refrigerated, within 15 hours of asystole death.

(3) Transport conditions of the human blood and blood components, human tissues and human cellular therapy products, unless otherwise validated by the manufacturer or specified within product specific Orders made for the purposes of section 10 of the Act, should be no more than 72 hours in duration, and temperature maintained within the range of

(a)	if refrigerated	2°C to 8°C
(b)	if frozen	less than minus 20°C
(c)	if cryopreserved	less than minus 40°C .

(4) Storage conditions of the human blood and blood components, human tissues and human cellular therapy products must be determined and validated by the manufacturer including, at minimum, temperature and duration of storage, unless otherwise specified in product specific Orders made for the purposes of section 10 of the Act.

(5) The product release bioburden specifications must include:

(a) the absence of microorganisms; or

(b) the absence of specified microorganisms of clinical significance; or

(c) the surveillance and control measures for minimisation of microbial contamination of the product during collection and manufacture; or

(d) the respective product specific Order where requirements are specified; and

(e) when the product is subject to terminal sterilisation or when the product is labelled as sterile, Annex 1 of the Code of GMP for Medicinal Products applies.

12. Requirements in relation to substances used in collection and manufacture

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

(2) Critical materials used in the manufacture of human blood and blood components, human tissues and human cellular therapy products that are:

(a) solutions, which contact the human cells or tissue during collection, processing, storage or transport, other than the antimicrobial agents used in a cell or tissue cleaning process validated by the manufacturer, must be:

Comment [m6]: EP/BP monograph for Plasma for Fractionation states that "the total period of time during which the temperature exceeds -20C does not exceed 72 h". The proposed TGO appears to be more stringent than the monograph in that it states that transport (of plasma for fractionation) should be no more than 72 hours in duration. This wording should be consistent.

Comment [m7]: This is inconsistent with Council of Europe, 15 Ed section, Chapter 5, Section 4 for storage of plasma (2-6 C) and shipping/transport of plasma (2-10 C).

(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 Register;

(b) antimicrobial agents used in a cell or tissue cleaning process validated by the manufacturer that are not supplied sterile should be passed through a 0.22µm filter prior to use in the manufacture of these products;

(c) material containing any components of human or animal origin, other than the starting materials of blood, cells or tissue, must have been sourced, tested (if methodology is available) and assessed as presenting a minimal risk of transmitting infectious disease agents in accordance with the requirements set out in the following documents:

(i) *TGA approach to minimising the risk of exposure to Transmissible Spongiform Encephalopathies (TSEs) through medicines and medical devices*, published by the Therapeutic Goods Administration; and

(ii) EMEA guidance document entitled *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), published by the EMEA at <http://www.emea.europa.eu/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf>; and

(iii) 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*, published by the EMEA at <http://www.emea.europa.eu/pdfs/human/bwp/026895en.pdf >

(d) If the substance is not required to be on the Register, the recorded information must include at minimum:

(i) screening tests performed;

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

(iii) storage conditions.

(e) If the information specified in Section 12 (2)(d) is not available from the manufacturer of the material, the material must be assessed by the manufacturer of the human blood and blood component, human tissue or cellular therapy.