Comments on Draft TGO XX- Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies.

Octapharma understands that the TGA regulates plasma derivatives as prescription medicines for which the default standard in Australia is the British/European Pharmacopeia (BP/EP). The BP/EP includes a monograph for 'Plasma for Fractionation', which is considered the appropriate standard. The monographs include a reference to the European Commission Directive 2004/33/EC that outlines in Annex III the eligibility criteria for donors of whole blood and blood components. These criteria are similar but not identical to those proposed by the Standard. In addition, the TGA mandates the use of the European Medicines Agency's Plasma Master File for the regulation of plasma raw material, and the EMEA's Note for Guidance on Plasma-Derived Medicinal Products, both of which address measures to minimise infectious disease risk though appropriate donor selection and testing. Thus 'plasma for fractionation' already has a distinct regulatory framework with requirements that are reasonably harmonised across international standards.

The proposed TGO appears to represent a change from the current harmonised situation as the document introduces Australian specific requirements that will make it difficult for overseas manufacturers (already meeting global regulatory requirements) to access the Australian market. Furthermore, implementation of the proposed requirements would not only would it make it difficult for overseas manufacturers to access the market but it would make it very difficult for importers to address shortages of domestic life saving products, such as intravenous immunoglobulin.

Below are specific comments in relation to plasma for fractionation that are proposed in the draft TGO:

Schedule 2 – Policy

In relation to point (4), Octapharma query whether TGA expect a microbial specification for each unit of plasma for fractionation. This would be a unique requirement relative to international standards and would also not be feasible.

Schedule 3 – Medical & Social History

Several criteria listed in Table 2 of the draft TGO are not consistent (highlighted in red text) with international requirements, and would require global companies to incorporate Australian specific selection procedures for donors outside Australia. For overseas manufacturers it would not be feasible to introduce Australian specific measures on top of their other global regulatory requirements. A summary of the differences between the TGO proposed criteria and the EU and US requirements in relation to 'allogeneic blood and blood components' (being the most applicable to plasma for fractionation) is provided in Table 1.

- Several of the criteria (i, k, o, p) are not reflected in the EU and/or US requirements
- Criteria (m) and (n) appear to be intended for cell and tissue donors
- Point (5) is stated as being applicable to “a potential donor of allogeneic tissues or cells…”; however, point (5) is specified as being applicable to plasma donors in Schedule 1 and also appears to be applicable to plasma donors in relation to criteria (u) in Table 2.

Table 1: Minimum medical and social history criteria required to define a donor's risks

	Period of ineligibility prior to donation for allogeneic use		
Criteria as defined by TGA draft order	**TGA requirement (Draft TGO)**	**EU Directive requirement (2004/33/EC, Annex III – Eligibility criteria for donors)**	**US requirement** (CFR Part 640, Additional standards for human blood and blood products, and CFR Part 610.40 Testing Requirements for communicable disease agents) • FDA Guidance for Industry (Implementation of Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for User in Screening Donors of Blood and Blood Components) • Full-Length Donor History Questionnaire, version 1.3 and Blood Donor Education Materials and Medication Deferral List
(a) Tattoo or body piercing	6 mths	6 mths, or 4mths provided a NAT test for HCV is -ve	Nil (if performed in a licensed facility; otherwise 12 months)
(b) Acupuncture	6 mths (unless performed by a licensed practitioner using sterile non-reused needles/equipment then nil exclusion period)	6 mths, or 4mths provided a NAT test for HCV is –ve (unless performed by a qualified practitioner and with sterile single use needles)	Nil
(c) Needle stick injury, or contact of non-intact skin or mucous membrane with blood and body fluid	6 mths when injury/contact is thought to be high risk of carrying HBV, HCV or HIV	6 mths, or 4mths provided a NAT test for HCV is –ve	12 mths from the date having an accident needle stick
(d) Inmate of a prison	12 mths from date of release (when imprisoned for consecutive period of 72hrs or more)	Defer after cessation of risk behaviour for a period determined by the disease in question and by availability of appropriate tests	12 mths from the date of release (when in juvenile detention, lockup, jail, or prison for more than 72 hours)
(e) Sex worker, or received money for sex	12 mths from last contact	Permanent (for 'persons whose sexual behaviour puts them at high risk of acquiring severe infectious diseases that can be transmitted by blood')	12 mths from last contact
(f) Male to male sexual relationship	12 mths from last contact	Defer after cessation of risk behaviour for a period determined by the disease in question and by availability of appropriate tests	12 mths from last contact

		or Permanent (for 'persons whose sexual behaviour puts them at high risk of acquiring severe infectious diseases that can be transmitted by blood')	
(g) Sexual relationship with a person known to: • Have HCV • Have HIV • Be a sex worker • Have male to male sex	12 mths from last contact	Defer after cessation of risk behaviour for a period determined by the disease in question and by availability of appropriate tests or Permanent (for 'persons whose sexual behaviour puts them at high risk of acquiring severe infectious diseases that can be transmitted by blood')	12 mths from last contact
(h) Ever injected any drug for a non-medical reason	permanent	permanent	Permanent
(i) Recipient of: • Human derived clotting factors • Viable animal cells/tissues	permanent	Permanent for xenotransplant recipients No similar criteria is defined in the EU regulations for recipients of human derived clotting factors or viable animal cells/tissues	Permanent for use of clotting factor concentrates No similar criteria is defined in the US regulations for recipients of viable animal cells/tissues
(j) Known to be infected with: • HCV • HIV • HTLV 1/HTLV 2	ineligible	permanent	Permanent
(k) Suspected to be infected with: • HCV • HIV • HTLV 1/HTLV 2	Ineligible until disease free state can be established	Defer after cessation of risk behaviour for a period determined by the disease in question and by availability of appropriate tests	No similar criteria is defined in the US regulations
(l) Known, suspected or at risk of being infected with HBV	Ineligibile until 1. Disease resolved (donor immunised or HBsAb≥100IU/L, or 2. As prescribed for risk factors (a) to (h)	Permanent, except for HBsAg –ve persons who are demonstrated to be immune or Defer after cessation of risk behaviour for a period determined by the disease in question and by availability of appropriate tests (for persons at risk)	Permanent or until disease resolved
(m) Physical evidence of sepsis	Ineligible until disease free state can be established	No similar criteria is defined in the EU regulations.	No similar criteria is defined in the US regulations.

			This criteria is not relevant for blood/plasma donors.
(n) Active infection of cells/tissue to be retrieved, active infection of other cells/tissues that are indicative of infection that render target cells/tissues unsuitable for manufacture	Ineligible until disease free state can be established	This criteria is not relevant for blood/plasma donors.	This criteria is not relevant for blood/plasma donors.
(o) Active infection of tuberculosis	Ineligible until disease free state can be established	2 yrs following date of confirmed cure	No similar criteria is defined in the US regulations.
(p) Typhus	Ineligible until disease free state can be established	No similar criteria is defined in the EU regulations.	No similar criteria is defined in the US regulations.
(q) Risk of prion disease	permanent	permanent	Permanent
(r) Recipient of human pituitary derived growth hormone	permanent	permanent	Permanent
(s) Recipient of allogeneic organs or cells, or deceased donor tissue allograft	permanent	6 mths, or 4mths provided a NAT test for HCV is –ve	12 months
(t) Recipient of allogeneic blood, blood components or blood products that do not meet the requirements of this order	12 mths unless there is a risk of prion disease or recipient of human pituitary derived growth hormone, then permanent	6 mths, or 4mths provided a NAT test for HCV is –ve	12 months
(u) Recipient of live vaccines or HepB vaccine	Ineligible from between 4 wks to 12 mths (for an unlicensed vaccine) depending on the live vaccine No deferral for Hep B vaccine if well and no exposure has occurred.	4 wks (live vaccines) No deferral for Hep B vaccine if well and if no exposure	Ineligible for 8 wks

Schedule 5 – Donor testing and examination

Table 2 below summarises (for blood/blood components for alloegeneic use only) the donor testing requirements proposed in the TGO draft document and those adopted internationally. It appears that the donor testing requirements are generally the same internationally with the exception of HBcAb and HTLV for blood and blood components in the EU (differences highlighted in red). It would not be practical or economically feasible for overseas manufacturers using EU donors to include this additional testing specifically for Australia. It is also noted that the draft TGO suggests that both HBcAb and HBV NAT testing will both be required; however, from a personal discussion with Glenn Smith it was indicated that the intention of the document was that one or the other test would be required. Clarification on this point would be welcomed.

Table 2: Donor testing and examination requirements for allogeneic donations for blood/blood components

Criteria as defined by TGA draft order		TGA requirement (Draft TGO)	EU Directive requirement (2002/98/EC, Annex IV Basic testing requirements for whole blood and plasma donations) or fractionators requirement (if not defined in EU Directive)	US requirement (Circular of Information for the use of human blood and blood components)
Serology, initial sample	Anti HIV-1 Anti HIV-2	Mandatory and samples tested must be non-reactive	Mandatory and samples tested must be non-reactive	Mandatory and samples tested must be non-reactive
	Anti HCV	Mandatory and samples tested must be non-reactive	Mandatory and samples tested must be non-reactive	Mandatory and samples tested must be non-reactive
	HBsAg	Mandatory and samples tested must be non-reactive	Mandatory and samples tested must be non-reactive	Mandatory and samples tested must be non-reactive
	HBcAb	Mandatory and samples tested must be non-reactive. (Reactive sample is acceptable only if HBsAb when tested is ≥100IU/L, or a specified recipient is known to be immune to HBV.)	Not mandatory	Mandatory for whole blood donations and samples tested must be non-reactive; not mandatory for plasma for fractionation (which is consistent with Table 4 of the draft TGO document for 'plasma only donors)
	HTLV 1/2 (antibodies)	Mandatory and samples tested must be non-reactive	Not mandatory	Mandatory for whole blood donations and samples tested must be non-reactive; not mandatory for plasma for fractionation (which is consistent with Table 4 of the draft TGO document for 'plasma only donors)
	syphilis	Mandatory and samples tested must be non-reactive.Non specific syphilis tests are prone to false positive results thus specific syphilis testing must be conducted on donors	Mandatory for whole blood donations and samples tested must be non-reactive; not mandatory for plasma for fractionation; donors tested in regular intervals.	Mandatory for whole blood donations and samples tested must be non-reactive; not mandatory for plasma for fractionation (which is consistent with Table 4 of the draft TGO document for 'plasma only donors); donors tested in regular intervals
NAAT, initial samples	HIV	Mandatory and samples tested must be non-reactive	Mandatory and samples tested must be non-reacitve	Mandatory and samples tested must be non-reactive
	HCV	Mandatory and samples tested must be non-reactive	Mandatory and samples tested must be non-reacitve	Mandatory and samples tested must be non-reactive
	HBV (when approved)	Mandatory and samples tested must be non-reactive	Not mandatory	Not mandatory