Blood and Tissues Unit
Office of Devices, Blood and Tissues
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

Attn : Dr Glenn Smith

Re: Proposed 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*

The Plasma Protein Therapeutics Association (PPTA) appreciates the opportunity to comment on this proposed Standard through a submission after the official consultation period. PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies. PPTA members provide 60 percent of the world's needs for Source Plasma and plasma protein therapies. In Australia, members of the global PPTA provide a significant proportion of the products prescribed for the treatment of haemophilia, immune deficiencies and other rare disorders, as well as products used to protect the health of pregnant women and babies. PPTA members are committed to assuring the safety and availability of these medically needed life-sustaining therapies.

The PPTA recognizes the Therapeutic Goods Administration as a peer authority committed to the common goals of assuring safety, quality and efficacy and drawing for

its regulatory measures on evidence and the continuing efforts to ensure harmonization in regulatory requirements. The PPTA is, therefore, concerned that the proposed ***Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies*** (http://www.tga.gov.au/bt/consult/drbloodstandards-tgoinfectious.pdf)(the Standards) undermine these principles if they are applied for plasma for fractionation in their current form. The wording of the Standards appears to imply that they do apply for plasma for fractionation, despite the statement on the TGA's web site that "***'Blood components' does not include products derived through fractionation of plasma"*** (http://tga.gov.au/bt/blood.htm)***.*** The PPTA concurs fully with this latter statement, holding the universally accepted view that plasma products are distinct from blood components manufactured in blood banks. One of the key distinctions lies in the nature of the raw material – plasma for fractionation – which has its own regulatory framework, distinct from that of fresh plasma transfusion, in most regulatory jurisdictions. It is puzzling, therefore, that the Standards include requirements for plasma donors within a document which is clearly worded and aimed at the areas of blood bank, tissue and cell therapy manufacture. It is unclear what relationship, if any, these Standards have to the current Therapeutic Goods Order 81 - STANDARDS FOR BLOOD AND BLOOD COMPONENTS (http://tga.gov.au/legis/tgo/tgo81.htm) - which, through the definition *"Blood components means* ***therapeutic*** [PPTA's emphasis] *components of blood (red cells, white cells, platelets, plasma)"* appears to exclude plasma for fractionation, which is a raw material, not a therapeutic. Clarification on this point is desirable.

The PPTA notes that the TGA regulates plasma derivatives as medicines, and that the default standard for medicines in Australia is the British (European) Pharmacopeia (BP). The BP includes a Monograph for Plasma for Fractionation, which, the PPTA assumes, continues to be the standard for this material, and which specifies the measures required to address the issues of relevance to the Standards. Included in this monograph is reference to the European Commission Directive 2004/33/EC (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:091:0025:0039:EN:PDF), which includes donor infectious disease minimization issues similar (but not identical) to

those proposed by the Standards. In addition, the TGA mandates the use of the European Medicines Agency's Plasma Master File for the regulation of plasma raw material, which addresses the issues of donor selection and testing for the minimization of infectious disease risk. Furthermore, the TGA mandates adherence to the European Medicine Agency's Note for Guidance on Plasma-Derived Medicinal Products, which includes measures to minimize infectious disease risk though appropriate donor selection and testing.

The PPTA presumes that the TGA is satisfied that the plasma products it has approved for the Australian market are conformant to all these mandatory international standards, and commends the TGA for aligning to the same standards that the global plasma products industry has to adhere to in order to maintain an international market. It seems that the proposed Standards represent a deviation from this pro-harmonization stance, and attempt to introduce another layer of regulation through Australia-only measures. It is therefore necessary to assess what these Standards contribute to the safety of the products which are the end result of the fractionation of plasma. The safety of such products is assured through a multilayered approach which includes the principles of selection and testing of donors as expressed in the Standards, but which also includes mandated and validated pathogen elimination techniques. It is these techniques which have ensured that blood borne pathogens have not been transmitted by products from the PPTA companies for the past two decades. The PPTA requests any risk assessments which the TGA may have performed in relation to these Standards' capacity to enhance the safety of plasma derivatives marketed in Australia, over and above the substantial safety measures ensured from the internationally accepted measures outlined in the other standards specified above.

Specifically, in relation to plasma for fractionation, these Standards precipitate tension with the following areas embedded in the TGA's currently mandated measures:

Schedule 2 – Policy

- The PPTA appreciates the TGA's need to ensure that consent for donation within Australia must conform to the applicable laws in the Federation. International standards including those cited above ensure that this occurs for plasma donors. In addition, individual countries have requirements to which collectors cited in those countries conform. However, expecting that the plasma raw material for fractionation for all products manufactured outside Australia is additionally conformant to the laws of the ten Australian jurisdictions is unrealistic.

- The PPTA interprets (4) as requiring a microbial specification and an associated release criterion for each unit of plasma for fractionation. If this is so, it constitutes a totally unique requirement relative to international standards e.g. the BP Monograph, and is unfeasible. Clarification would be welcome.

Schedule 3 – Medical and social history

Several of the criteria in Table 2 are not reflective of international requirements, necessitating further questions in any selection procedures applicable outside Australia. This is unfeasible, and unnecessary considering that these procedures are adopted by the TGA.

- Criterion (a) in Table 2 is not reflective of the requirements of the EC Directive and the Council of Europe Guide, which are linked to TGA requirements for plasma for fractionation and for blood components.

- Criterion (d) is not reflected in any international standard for donors of plasma for fractionation.

- Criterion (l) is not reflective of the EC Directive's requirements. Referral to the other criteria is confusing as these vary in their requirements.

- Criteria (m) and (n) are clearly intended for cell and tissue donors – it is difficult to see these being incorporated into a donor questionnaire for plasma donors.

- (5) is specified as applicable to "*A potential donor of allogeneic tissues or cells*" but is specified as applicable to plasma donors in Schedule 1. Clarification is required. If applicable to plasma donors, many of these vaccination criteria are unreflective of the other standards which the TGA adheres to.

Schedule 4 – Sampling, test kits, test protocols and test management

The archival requirement in (10) requires clarification if applicable for plasma for fractionation. The TGA will be aware that the expiry dates applicable for the different types of plasma for fractionation vary. Similarly, the expiry dates for product intermediates and final products also vary. This has the potential to generate an archival period for these samples which can last for many years and generate enormous inventories. Furthermore, the required archival of a sample taken 180 days post-donation has the potential to double the size of such an inventory. This measure, clearly linked to justifiable requirements in some areas of cell and tissue products, is irrelevant, unfeasible and not reflective of international practice for plasma derivatives.

Schedule 5 – Donor testing and examination.

The PPTA appreciates the recognition in the Standards that certain tests are clearly irrelevant to plasma products. These include the tests excluded from plasma only

donors in Table 4. However, the PPTA feels that further thinking is required in regards to antibody to hepatitis B core antigen (HBcAb). It is noted that the TGA is requiring HBcAb for blood components, an additional measure to current requirements. At the same time, the Standards correctly anticipate the imminent introduction of HBV NAT through the multiplex NAT assays used to screen blood. The economic viability of introducing HBcAb along with HBV NAT for fresh components is very dubious, and the PPTA presumes that such an expensive measure will be subject to cost-benefit analysis by other authorities in the Australian government. The PPTA's concern in introducing HBcAb at this stage lies in the effect this will have on the Australian plasma for fractionation used to manufacture domestic plasma products. The TGA will be aware that the US FDA does not require this test for plasma for manufacture (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062847.pdf), and states in justification:

"*PLASMA FOR FURTHER MANUFACTURE*
A. Source Plasma: The FDA does not currently recommend that Source Plasma donors be tested for anti-HBc. If anti-HBc reactive units were excluded from pools used for the manufacture of plasma derivatives, titers of anti-HBs in those pools would be expected to diminish, as both these antibodies usually occur together in plasma. The presence of anti-HBs is believed to contribute to the safety of certain plasma products such as the immunoglobulins. '
B. Recovered plasma: Plasma units that are untested, nonreactive, or repeatedly reactive for anti-HBc are currently acceptable for the manufacture of plasma derivatives"

The TGA may wish to consider this issue further, given the implications on the safety of final products. Furthermore, if introduced for the Australian pool with an ensuing decrease in the titer of HBcAb in the final immunoglobulin products, the PPTA is apprehensive of a repeat of the inexpert confusion which underpinned a similar issue involving overseas and domestic immunoglobulin some years ago (1,2). Given that the introduction of HBV NAT will address much of the residual risk of window period

donations for HBV in whole blood donors, which is already low in Australia due to the use of state of the art HBsAg assays, it would seem prudent to review the need for a concurrent introduction of HBcAb. It is known that preliminary studies by the Australia Red Cross in the late 1980's showed that a donor loss of 4% was to be expected through the introduction of HBcAb screening. At the very least, a risk benefit analysis for the introduction of this measure, incorporating data on the prevalence of occult hepatitis B[1] in Australia, should precede its introduction.

Conclusions

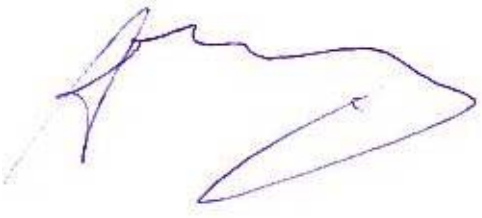
The PPTA commends the TGA for generating a set of requirements which are clearly needed and applicable in the field of tissue and cell donation, where the established safety paradigm for blood components and plasma derivatives is still lacking. It is clear, from the language and the actual measures proposed that the Standards are directed to this sector, and are not applicable to plasma products. Their imposition would represent a serious problem in access to plasma therapies for Australian patients, as it is difficult to see non-Australian manufacturers introduce Australia-only measures in their respective operations on top of the other global requirements which are also mandated in Australia. In addition, the introduction of further measures, including HBcAb, in the domestic sector will increase the costs for Australian payers and possibly affect the safety of domestic products. The PPTA is aware of the option of seeking an exemption from these Standards under Section 14 of the Therapeutic Goods Act. However, the PPTA is disinclined to advise its member companies to seek an exemption, which would be public information, from a set of purported safety measures when the problem is embedded in the unsuitability of these Standards. Therefore, the PPTA requests that the TGA makes it clear that these Standards are applicable to the areas of cell and tissue therapies, which are currently subject to very little oversight for their safety, unlike

[1] The introduction of HBcAb screening may pick up the small number of donors with circulating HBV DNA at a concentration below the sensitivity of NAT and in the absence of HBsAg. The prevalence of such donors must be presumed to be very low, and as NAT assays increase in sensitivity, they will be detected by NAT, as will donors in the pre-seroconversion window.

plasma products which are already subject to a comprehensive and effective safety framework.

The PPTA would be pleased to engage further with the TGA on this issue. An acknowledgment to this submission would be appreciated.

Sincerely



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6 April 2010

References

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