# ANZTPA: Description of a possible joint regulatory scheme for therapeutic products under ANZTPA

## EBAANZ Feedback on January 2013 Discussion Paper

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Background

Eye Bank Association of Australia and New Zealand (EBAANZ) is the peak body for eye donation and transplantation in Australia and New Zealand, representing all eye banks in Australia and New Zealand that provide the service of eye donation for the purpose of corneal transplantation. EBAANZ also has representation in the Australian and New Zealand Corneal Society (the special interest group on cornea and eye banking of the Royal Australian and New Zealand College of Ophthalmologists). EBAANZ’s purposes include:

- the facilitation of the safe availability of corneal and other ocular tissues required for transplantation in Australia and New Zealand;
- to provide representation to government agencies, health entities, community organisations, medical and industry groups as well as the general public in regard to eye donation and corneal transplantation; and
- to provide a framework for the sharing and distribution of ocular tissue required for transplantation across Australia and New Zealand

The possible joint regulatory scheme for therapeutic products under ANZTPA has a direct impact on the operations and sustainability of eye donation and corneal transplantation across Australia and New Zealand. Please find attached our comments.

As a key stakeholder in the ANZTPA project, EBAANZ has prepared this submission which addresses the key aspects of the proposed framework and the likely impact on eye banks in Australia and New Zealand. Comments in this submission are restricted to EBAANZ’s area of expertise – Biologicals (human cell and tissue-based therapeutic goods). The professional services of eye banks in Australia have been regulated under the Therapeutic Goods Administration (TGA) since the mid-1990s and, more recently, our member organisations have experienced first-hand the implementation of the Biologicals Regulatory Framework that came into effect on 31 May 2011.

In addition, as a professional society that represents members in Australia and New Zealand, EBAANZ has an in depth knowledge of eye donation, eye banking and corneal transplantation as it is practiced on both sides of the Tasman and the current level of integration, information, and established standards that are shared between regions.
EBAANZ Summary Statements

- EBAANZ is supportive of a joint Australian and New Zealand scheme for the regulation of organs, eyes and tissues for transplantation to be administered by an appropriate regulatory agency.

- Internationally, it is unusual for eye and tissue donation and transplantation to be regulated as a therapeutic good by a therapeutic goods agency (as pharmaceuticals and medical devices). The one exception is Australia. Eye and tissue donation is usually regulated as a clinical service by a Human Tissue Authority or equivalent.

- The regulation of biologicals described in the ANZTPA discussion paper requires compliance with a code of Good Manufacturing Practice. This approach is currently unique to Australia and is not reflected internationally. Internationally, audited adherence to agreed standards is required (and in the USA adherence to a code of Good Tissue Practice to distinguish these items from manufactured therapeutic goods).

- EBAANZ does not support the joint regulation of biologicals as described in the January 2013 discussion paper. Importantly, it differs significantly from the original 2007 ANZTPA consultation documents. Thus significant issues need to be addressed with key changes made to the proposal.

- EBAANZ recommends the degree of regulation applied to a biological is commensurate with the inherent risk in the transplant of the tissue (the discussion paper framework does not do this well), and also the benefit and availability of the donated transplant tissue. The size and commercial status of the organisations being regulated should also be considered.

- Standards and requirements under a joint biological regulatory scheme must be the same on either side of the Tasman to prevent an inequitable duplicity and Australia-only, New Zealand-only manufacturing and product licenses.

- Over-regulation (that is not commensurate with degree of risk of use of donated human ocular tissue) has placed an inequitable strain on eye banking resources and infrastructure in Australia. Direct government financial support has been required to ensure the continued viability of donation and transplantation. Implementation of the ANZTPA Framework as described will extend this situation across the Tasman and require substantial subsidy and support from the New Zealand government.

- Due to the current regulatory scheme, product has been withdrawn from the Australian market. This now requires the importation of biologicals from overseas under the Special Access Scheme, increasing risk and costs to the community. Implementation of the ANZTPA Framework as described will extend this situation across the Tasman.

- The infrastructure for eye and tissue donation in New Zealand is less developed and more centralised than in Australia, making it especially vulnerable to over-regulation. Regulating biologicals as described in the ANZTPA discussion paper will reduce the availability of corneal tissue for transplantation in New Zealand and possibly threaten the viability of eye banking and corneal transplantation in New Zealand.
Support for joint regulation of therapeutic products under ANZTPA

The development of a new joint Trans-Tasman regulatory scheme provides an excellent opportunity to review the strengths and weaknesses of the regulation of therapeutic products in Australia and New Zealand, and then to draw on our collective expertise and experience to design an efficient, appropriate and responsible regulatory regime. EBAANZ is supportive of an appropriate scheme for the joint regulation of organs, eyes and tissues for transplantation to be administered by a joint agency where the organs, eyes and tissues are appropriately regulated in Australia and New Zealand.

This is an opportunity not to repeat the mistakes of the past and not merely to continue unquestionably with the Australian status quo. In Australia, by the end of the transition phase of the Biologics Regulatory Framework, all biologicals that meet the definition of a therapeutic good must be included on the Australian Register of Therapeutic Goods (ARTG) before they are supplied in, imported to, or exported from Australia, unless they are excluded from TGA regulation, are declared to not be a biological, or are exempt and otherwise authorised or approved (such as under the Special Access Scheme). Eye banks in Australia are already experiencing significant issues in achieving the level of regulatory compliance required under the Biologics Regulatory Framework. In New Zealand, however, biologicals have not been previously regulated under a therapeutic goods scheme, and there is now an opportunity to start with a clean page and draw on and learn from the experiences of others.

Level of support for the proposed ANZTPA joint regulatory scheme

The discussion paper indicates the content of the possible regulatory scheme “takes as its starting point the draft ANZTPA Rules in relation to which consultation took place in 2006 prior to the 2007 postponement of the previous Australian-New Zealand negotiations” (page 7). However, the proposed regulation of biologicals differs in some significant aspects from that developed during the initial ANZTPA consultations of 2006 and 2007, and indeed mirrors the TGA’s Biologics Regulatory Framework that came into effect in Australia on 31 May 2011.

These changes have altered the level of regulation that the original authors (in consultation with the expert stakeholders) felt was commensurate with the potential risks to public health and safety. It also invalidates some of the conclusions of the TGA’s Regulatory Impact Statement (RIS) which were based on implementing a level of regulation commensurate with the degree of risk inherent in the use of a product. The option initially recommended by the TGA in the 2004 RIS specifically noted that “this option would have minimal impact on eye and tissue banks in Australia because they are already required to comply with a cGMP for Human Blood and Tissues” and “the development of a cGMP for HCT/Ps would not be a major impost to eye and tissue banks as the standards file that would need to be submitted to the TGA would draw heavily on the information that eye and tissue banks are already required to hold as part of their cGMP compliance”. However, this is not the regulatory scheme and regulatory requirements that were delivered in the Biologics Regulatory Framework. As a result of the implementation of the Biologics Regulatory Framework, the direct/indirect regulatory costs incurred by eye and tissue banks for the registration of a biological on the ARTG, as well as the newly imposed overly restrictive regulatory requirements, has already threatened the viability of some tissue banks in Australia (refer to section x for more details).

As such, EBAANZ does not support the joint regulation of biologicals as described in the January 2013 discussion paper. This submission will clarify EBAANZ’s reasoning and the likely impact on eye
donation in Australia and New Zealand if the regulation of biologicals is implemented as described in the January 2013 discussion paper.

**EBAANZ does not support the joint regulation of biologicals as described in the January 2013 discussion paper. Significant issues need to be addressed with key changes made to the proposal.**

**Eye banking regulations in Australia and New Zealand**

In Australia, human tissues and cellular therapies are now regulated under the TGA’s Biologicals Regulatory Framework. This requires eye banks to adhere to a code of good manufacturing (cGMP) practice for blood and tissues, and the intent to list the risk “products” (i.e. cornea for transplantation and sclera for surgical use) on the Australian Register of Therapeutic Goods. In New Zealand, eye banking is regulated under those provisions that relate to the clinical practice and the practice of medicine in that country. All Australian and New Zealand eye banks adhere to standards that are consistent with international best practice.

Thus, the proposal to include biologicals as described in the ANZTPA discussion paper would, for the first time, subject New Zealand eye and tissue donation and transplantation to a cGMP and product standard regime. This is an approach that has been successfully applied to manufactured therapeutic goods (i.e. pharmaceuticals and medical devices) but for tissues it is an approach that, internationally, has been adopted only by Australia.

In addition, it is also unusual for the regulatory body overseeing tissues to be the same agency that regulates pharmaceuticals and medical devices; the exceptions are Australia’s TGA and the United States (the Food and Drug Administration that of course has a wide ranging ambit including food).

**The ANZTPA approach to biologicals regulation (cGMP and product standards through Therapeutic Goods Orders) is unusual and unique in the world.**

**Regulation of tissues and cellular therapies by the same organisation that regulates pharmaceuticals and medical devices is unusual and matched, internationally, only by the United States FDA (which has responsibilities for regulation beyond that of therapeutic goods).**

**Classification of Biologicals**

It is extremely important to place a biological within an appropriate Class to ensure that the level and application of regulation are appropriate. This is necessary to ensure appropriate and achievable standards are implemented, compliance remains possible and efficiencies with the system are maintained.

The TGA’s Biologicals Regulatory Framework uses different criteria for determining a product’s class than the criteria originally described in the 2007 ANZTPA consultation. This difference has been incorporated in the classification of biologicals described in this ANZTPA discussion paper. Consequently, risk is now clumsily and erroneously ascribed. In addition, in its pre-market regulation of biologicals, there is now little or no difference in the regulatory requirements between classes, resulting in over-regulation (based on risk) of Class 2 Products. These issues and the now-realised impact on stakeholders are discussed in further detail in the following sections.
The actual pre- and post-market assessment and controls applied to each Class are barely distinguishable from one another (especially between Class 2 and 3).

The implementation of the TGA’s Biologicals Regulatory Framework, upon which the ANZTPA framework is based, has resulted in inefficient and costly over-regulation (based on risk) of Class 2 biologicals, threatened the viability of eye banking and tissue banking in Australia and reduced access to the Australian community of well-established and safe therapeutics (which are now imported to meet need).

Classification according to Risk
As already stated, the Biologicals Regulatory Framework implemented in Australia (mirrored in the regulation of biologicals in the ANZTPA discussion paper) differs in some significant aspects from what was developed during the initial ANZTPA consultations of 2006 and 2007.

The framework described in the ANZTPA discussion paper applies “different levels of pre-market regulation to biological products based on the risks associated with the use of each product”(1). However, our knowledge of the framework upon which the ANZTPA framework is based demonstrates that, in its current format, the framework will not achieve these aims. The system is not refined or implemented well enough to both define and discriminate between levels of risk.

Under the proposed ANZTPA Framework, the definitions that determine a particular Classification Level of a biological are unclear (particularly in reference to Class 1 and 2). There is a requirement for a better understanding of exactly what risks are involved (biological or technological), the demonstrated level of risk, what contributes to risk, and a better understanding of the properties of the biologicals the Classification system is attempting to define. Therefore clarification is needed within the framework in regard to defining risk and risk in association with degrees of manipulation.

For example, the ANZTPA framework does not allow for the significant differences in risk and manufacture between eye tissue and other allograft tissue such as heart valves and bone. Corneas are provided as a Class 2 example along with heart valves, yet the degree of infectious disease risk and the degree of manipulation of these two “products” are demonstrably different. For example, corneas are time-sensitive in their use (like organs, their timeframe is days rather than months), while heart valves are able to be used after 5 years of storage.

Placing these two products in the same Class creates a mismatch with regulatory requirements, making compliance not only overly onerous but in some instances also not possible. These problems were clearly highlighted by the necessity to provide exceptions for eye tissue in the Australian cGMP - Human Blood and Tissues (2000)(6) (e.g. exceptions for NAT testing and bio-burden testing).

The proposed ANZTPA framework also provides no indication on how risk is defined or how risk is assessed (Class 1 being low-end and Class 4 being high-end). The highest risk from a biological is the risk of infectious disease transmission, yet it does not seem that the classification system has its underpinnings in this risk. For instance, the proposed Framework classifies corneas as a Class 2 biological, yet this is a biological with significantly less demonstrated risk and theoretical risk of infectious disease transmission than any other organ or tissue and has the same clinical oversight as that of organ donation and transplantation.
If corneas are not classified as Class 1, it is difficult to envisage any biological that would be classified as Class 1 and therefore the Class becomes redundant.

If the ANZTPA Framework adopts the approach to Product Standards as outlined in the TGA’s Biologicals Regulatory Framework, it allows for an all-encompassing Therapeutic Good Order (TGO) for minimising infectious disease transmission. This erroneously assumes that the risks, vectors, and infectious disease agents are the same for all biologicals, thus creating another mismatch between regulatory requirements and human biology.

*Standards (TGOs) designed to minimise infectious disease transmission should be incorporated within the Standards (TGO) that applies to a specific product grouping. This avoids a conflict between Product specific standards and infectious disease standards and applies appropriate approach to the product based on risk of use of the product (the stated aim of the ANZTPA framework).*

In the absence of a risk assessment based on transmission of disease within the ANZTPA Framework, risk appears to be correlated with “degree of manipulation” i.e. those biologicals that are subject to a higher degree of manipulation are considered higher risk. Such a correlation may be appropriate for manufactured products such as pharmaceuticals or medical devices. However, for a homologous transplant most of the risk derives from the donor themselves rather than any post-retrieval “processing” or manipulation. For any remaining risk, the definition given within the Framework for “minimal manipulation” is too generalist and all-encompassing to be used as fine discriminator of risk.

The TGA itself recognised while formulating the original draft of the Biologicals Regulatory Framework that “A number of different factors influence the overall level of risk posed by an HCT/P and it is not a strict linear relationship between the level of manipulation of the tissue or cell and the level of risk posed. These different factors include: the source of the tissue; the proposed function of the tissue in the patient; the nature of the tissue or cell processing; and the viability of the finished product”\(^{(4)}\). However, these principles did not find their way into the TGA’s final Biologicals Regulatory Framework.

These principles need to be reintroduced to provide for better discrimination between lowest, low risk and higher risk biologicals. Importantly, it needs to incorporate the concept of whether or not the living properties of the biologicals have been deliberately altered during processing for storage or other purpose (i.e. altered from their living state and functions). Freezing, or other forms of long-term storage, deliberately alters the properties of a biological and are higher risk than those biologicals where the properties remain unaltered.

*Organs*

The proposed biological regulatory scheme described in the ANZTPA discussion paper also specifically excludes “fresh viable human organs”. This is consistent with the current approach in Australia, although the original intent of the TGA (and the original ANZTPA consultations of 2004) was to include human organs in the regulations\(^{(4)}\). The reason for the exclusion in Australia was based on a decision of the Australian Health Ministers Conference (AHMC) that deemed “human organs were adequately managed by other methods”. This referred to the Cognate Committee on Organ and Tissue Donation and Transplantation which was subsequently replaced by the Australian
Organ and Tissue Authority (AOTA). One of the responsibilities of AOTA is the National Eye and Tissue Donation Network\(^7\) (which essentially embraces those product types included in Class 2 of the proposed ANZTPA framework). New Zealand has no equivalent Authority. The TGA authored Resource Guide – Overview of the Biologicals Framework of October 2010 indicates that “The Biologicals Framework will not cover solid organs or assisted reproductive technologies (ART). The Australian Organ and Tissue Authority (AOTA) will continue to oversight solid organs while ART will continue to be regulated under the current arrangements”\(^8\).

Therefore the proposal to exclude “fresh viable human organs”, or indeed the proposal to include human tissues for transplantation that fall into Class 2 (eg. corneas sclera, skin), in the ANZTPA regulatory framework needs to be reviewed in accordance with:

- Does the “management by other methods” continue to fulfil the regulatory role for human organs, and now also fulfil the role for tissues for donation and transplantation?
- Does New Zealand have a mechanism to fulfil the same regulatory measures for “fresh viable organs” that are proposed to be excluded from ANZTPA regulations?
- Is the approach and organisation used for the regulation of the pharmaceutical industry and medical device industry appropriate for “publically funded not-for-profit hospital supply organisations” such as organ donor organisations, eye banks and tissue banks? Are organs and corneas therapeutic goods or are they human tissue provided through clinical and medical services?

These are not new questions; they were addressed by a joint TGA and Medsafe Consultation paper of 2007\(^2\). However, the answers in 2013 may now be different than they were in 2007. Medsafe in 2007 identified that (page 9)\(^2\):

- “the lack of formal requirements [in New Zealand] impacts on the ability to assure the safety of therapeutic products, such as whole organs for transplantation and the ability to track the use of a product should an adverse event occur”;
- “the lack of formal international harmonisation has implications for the sharing of whole organs between Australia and New Zealand”

It was in light of these considerations (organs and tissue) that “the New Zealand Government has proposed that the therapeutic uses of human tissue would be regulated under the Joint Therapeutic Products scheme to be administered by the ANZTPA”\(^2\).

Has the environment and governance arrangements changed on either side of the Tasman since 2007, and has there been a consideration of what should be regulated rather than a continuation of the Australian status-quo (which may not be suitable for New Zealand)?

In addition, it is important for the reasons discussed in the following sections that the approach and any inclusions/exclusions remain consistent on both sides of the Tasman.
**Level of Regulation**

Earlier ANZTPA consultations proposed a level of regulation for each biological Product Class that was based on a risk benefit analysis of the type of HCT. In 2007, ANZTPA proposed the following regulatory requirements(2):

- **Class 1**: Proposed declaration of compliance with relevant Standards which will be developed by the relevant sector
- **Class 2**: Demonstrated compliance with Standards and Manufacturing Principles
- **Class 3**: Demonstrated compliance with Standards and Manufacturing Principles and demonstrated safety, quality and efficacy of the Product (which requires the submission of a Product Dossier). The Dossier also needs to include all manufacturing, pre-clinical and clinical information to support the product.
- **Class 4**: Demonstrated compliance with Standards and Manufacturing Principles and demonstrated safety, quality and efficacy of the Product (which requires the submission of a Product Dossier). The Dossier also needs to include all manufacturing, pre-clinical and clinical information, and relevant clinical data and analysis to support the product.

Notably, a Class 2 biological would require submission to the regulatory authority of a *Standards File* (a document outlining the technical information that demonstrates compliance with Standards applicable to the relevant HCT) but a Class 3 or 4 biological would require submission to the regulatory authority of a *Dossier* (a document outlining all scientific and technical information to support the design and production of the biological).

However, the Biological Product approval process described in the ANZTPA discussion paper now requires an application to supply a Class 2 biological to demonstrate compliance with relevant Standards and Manufacturing Principles *in addition to submission of a Product Dossier*(1). Under the TGA’s Biologicals Regulatory Framework, a Class 2 biological also requires submission to the TGA of a Dossier that demonstrates the quality and safety of the biological; compliance with relevant Standards; suitability for the intended clinical use. The level of regulation for a Class 2 biological is disproportionate to the level of risk.

These changes have created (and will create for ANZTPA) a process and culture of regulation that the 2006 and 2007 ANZTPA consultations were specifically trying to avoid i.e. inefficient and costly over-regulation whereby the donation and transplantation of tissues must fit into the same paradigm of regulation as manufactured goods such as pharmaceuticals and devices. Indeed the reason for the development of the TGA’s Biologicals Regulatory Framework was a recognition that biologicals did not fit with the pharmaceuticals and devices approach to regulation(2).

One of the reasons for these additional requirements in the TGA framework is that certain requirements have to be met in order for therapeutic goods to be listed on the ARTG(8). These requirements of course relate to the original purpose of the ARTG – to list pharmaceuticals and devices. Thus, while the TGA’s Biologicals Regulatory Framework may have originally been designed to better fit the needs and regulatory approach required for biologicals, one of the intended outcomes of the regulation (listing them on the ARTG) means that *implementation* requires a pharmaceutical and device approach. Thus the purpose and intent of the Biologicals Regulatory Framework has been corrupted.
Given the available infrastructure, any mismatch between regulatory requirements and the dictates of human biology will be felt more in New Zealand than Australia, with the potential for increased risk to the viability of the biological and thus the potential for harm to the clinical needs of transplant services.

**ANZTPA has the opportunity to avoid this funnelling effect into the pharmaceuticals regulatory culture and approach by creating a listing for biologicals separate from that of pharmaceuticals and devices. Unlike the ARTG, the requirements for listing would be requirements that are appropriate for biologicals and not pharmaceuticals.**

**Trade between Australia and New Zealand**

The fundamental principle upon which the joint regulatory scheme is based is to “develop a more integrated trans-Tasman economy by removing regulatory impediments between Australia and New Zealand and to enable goods to be traded freely between them”\(^{(1)}\).

Therefore it is important that the same rules and orders apply equally to both countries to avoid the creation of “Australia-only” or “New Zealand-only” manufacturing licences or approved product listings. To do otherwise, not only negates the benefits derived from a joint scheme, but paradoxically has the potential to actually further restrict trade between the two countries. For example, corneas for transplant are now able to be freely imported into New Zealand from Australia. This is an important source of corneas for New Zealand to meet the occasional local shortfall in numbers for transplantation and most importantly for urgent cases of corneal transplantation. The introduction of country specific licences, as a result of differing standards or different implementation of rules or orders, would actually restrict the sharing between the two nations of this important sight-saving and sight-restoring human biological.

The creation of “Australia-only” and “New Zealand-only” manufacturing licences was flagged during earlier consultations regarding the joint regulatory framework in 2007. The issue related to the manufacturing licence requirements of laboratories providing testing services to a manufacturer of a biological. A decision was made that due to available infrastructure and resources, New Zealand laboratories providing testing services to a biologicals manufacturer would not have to hold an ANZTPA manufacturing licence (or indeed a Medsafe licence) but continue to be accredited under existing NZ pathology laboratory accreditation schemes, whereas an Australian laboratory would continue to be required to hold a relevant manufacturing licence (either an ANZTPA licence or a continuation of the TGA licence). This created different Standards and Rules for either side of the Tasman and would have led to New Zealand-only and Australia-only licensed product listings. The 2007 ANZTPA consultation document confirms that “…a licence applying only to one country - A licence with a condition of supply for only one country…”\(^{(2)}\) could be issued.

The proposed joint regulatory scheme described in the ANZTPA discussion paper indicates that such scenarios would still be acceptable under ANZTPA (paradoxically increasing trade barriers between the countries). For example, page 38 refers to “…biologicals are allowed to be supplied in Australia and/or New Zealand…..”\(^{(1)}\) and on page 40 the “Conditions on a Manufacturing Licence” indicate that ANZTPA will be able to impose special conditions on a manufacturing licence\(^{(1)}\).
These provisions, although undoubtedly designed to maintain flexibility and rational decision making on a case-by-case basis, should not be used in any ANZTPA framework to justify different standards or manufacturing requirements applying on either side of the Tasman.

*It is important that the same rules and orders apply and are implemented equally to both countries to avoid the creation of “Australia-only” or “New Zealand-only” manufacturing licences or approved product listings.*

*It should not be assumed that adopting the regulation of biologicals in accordance with the TGA’s Biologicals Regulatory Framework is appropriate for the New Zealand environment (i.e. the current Australian regulations should not become the de facto ANZTPA regulations).*

*Consideration of the resources and infrastructure available in both countries is required, and the development and implementation of regulations that is appropriate for both nations, not one or the other.*

**Costs and eye donation and corneal transplantation viability**

The costs involved in complying with the regulatory scheme from a stakeholder’s point of view are both direct and indirect. The ANZTPA discussion paper clarifies that ANZTPA will be funded on the basis of full cost recovery\(^{(1)}\) (similar to the TGA system) where “all activities undertaken by ANZTPA as part of pre-market, post-market monitoring and compliance and general enforcement activities in relation to therapeutic products regulated under the scheme will be funded by the collection of fees and charges”\(^{(1)}\). The indirect costs are those incurred by the eye bank or tissue bank in meeting the regulatory requirements, the majority of which are administrative labour costs. The higher the degree of regulation, the higher are the costs.

Both direct and indirect costs can be reduced by matching the degree of regulation to both the inherent risk in the transplant of the tissue and to also the size, commercial status and undertakings of the organisations being regulated. The current TGA’s Biologicals Regulatory Framework does not do this, and, by ANZTPA adopting the same unaltered framework, they would risk the same consequences now being realised in Australia.

The TGA Cost Recovery Impact Statement of February 2011 details the direct costs to be charged to the eye and tissue banks\(^{(5)}\). Notably the impacts of these costs were only discussed in the context of its impact on the TGA; the impact on the eye and tissue banks themselves was not addressed. The approach to cost recovery and regulation from small (1-10 staff members), publicly funded, legislated not-for-profit services by the TGA is the same as that for large multi-national publically listed pharmaceutical companies. The RIS prepared by the TGA in 2004 stated there would be minimal impact on eye and tissue banks as a result of implementing TGA’s recommended option for the regulation of HCT/Ps\(^{(4)}\). The TGA assessed there would be minimal impact on eye and tissue banks because, under the TGA’s recommended option, eye and tissue banks would be required to comply with cGMP for Human Blood and Tissues (which they were already required to do) and the requirement for eye and tissue banks to submit a standards file would be of minor impost as it would draw heavily on the information that eye and tissue banks already held as part of their cGMP compliance\(^{(4)}\).
However, the implementation of the TGA’s Biologicals Regulatory Framework, saw the direct cost involved in approval and registration of a Class 2 biological amounting to $83,300 AUD. These costs are comprised of an application fee, evaluation fee and annual charge per biological as well as an audit fee. For some Australian eye banks, these direct costs exceed 40% of their total yearly revenue (based on service fee recovery from annual number of transplants). Recognising the severe financial impost and threat to the viability of the eye banking and tissue banking services provided to the Australian community, the Commonwealth Government agreed to meet Non-profit hospital supply unit direct regulatory costs for the first three years of operations of the new framework.[5]

The indirect costs incurred by eye banks in complying with the regulatory requirements have increased since the Biologicals Regulatory Framework came into effect in 2011. Taking into account time and labour, a conservative estimate on the cost to an eye bank of preparing the applications for product licensing is $100,000 AUD (salaries and on-costs). Eye banks are spending upwards of 25% of their resources in meeting only their regulatory obligations. For eye banks, these are the costs of regulating a service that, since corneal transplantation began in Australia in the 1940s, has never transmitted a communicable infectious disease and not contributed to an injury to a recipient threatening life or disability.

The RIS prepared by the TGA in 2004 stated the impact on consumers as a result of implementing TGA’s recommended option for the regulation of HCT/Ps included the provision for eye and tissue banks to pass on to consumers any increase in cost as a result of complying with the new requirements. Furthermore, the RIS clarified “Where such costs can not be passed on to consumers (or where there are low volume products), it is possible that some products will be withdrawn from the market. At this stage it is not possible to estimate the extent of this risk (that is, number of products that could be affected and the impact on consumers). It is possible that this risk is low and that the more probably (sic) eventuality will be consolidation of activities and expertise within a more limited number of centres rather than in a number of very small operations in multiple hospitals/university laboratories”[4].

In fact, the consequences of the new Biologicals Regulatory Framework in Australia, even before it became operational had been:

- The imminent closure of a bone bank due to regulatory burden and costs making it unsustainable in the long run (Barwon Bone Bank).
- The withdrawal of the biological ‘amniotic membrane’ (a small turnover, non-commercial product) by the only holder of an TGA licence to manufacture, due to unsustainable direct and indirect regulatory costs and inability to meet regulatory criteria (yet still adhering to international standards). Amniotic membrane remains in demand and is now imported (under the special access scheme) to Australia from New Zealand.
- The non-renewal and withdrawal of a laboratory from TGA licensing for testing of biologicals due to the non-viable commercial nature of retaining a high-cost (financial and resources) licence for a small turnover service with insufficient financial returns (ALS Laboratories), further reducing options for testing services for biologicals.

In the context of medical devices and pharmaceuticals “withdrawal of some products” and “consolidation of activities and expertise within a more limited number of centres” may be acceptable. However, in the context of donation of tissues and organs for transplantation where there is often a shortfall in patient need, that are time-sensitive (as in the case of corneas), and
where local donation and transplantation provides superior transplant outcomes to “centralised supply”\(^{(9)}\), the withdrawal of any products and the closure of eye banks is not acceptable.

**The risks and impact of an equivalent regulatory framework under ANZTPA to New Zealand is greater than faced in Australia. Donation infrastructure is less well developed than Australia and thus more vulnerable to regulatory burden, and the lower population dictates single national agencies for eye donation and transplantation and for various forms of tissue banking.**

**In addition, accessibility to ANZTPA licensed testing laboratories for time-sensitive biological testing will be even more limited. A risk to the viability of an eye bank in New Zealand is a risk to the viability of corneal transplantation in New Zealand.**

Mitigation of these risks under ANZTPA will require one or all of the following:

- A reassessment of the levels regulation and regulatory burden, and a reassessment of risk versus benefit under ANZTPA rather than an automatic carry-over of the Australian regulatory status quo. This would mean an evidence-based review of the products in Classes 1-4 to match regulatory levels to both demonstrated and theoretical risk and benefit.

- A reassessment of the licensing requirements and level of regulation applied to laboratories contracted to provide testing services for biologicals (e.g. infectious disease donor screening and sterility testing services) in order to ensure consistency on either side of the Tasman and to ensure continued provision of these services to eye banks and tissue banks.

- Substantial government subsidies and/or concessions to meet both the direct and indirect costs of regulation to ensure the viability of donation and transplantation services in both countries.

- A consistent approach on either side of the Tasman in regards to government subsidies and support in order to avoid an “uneven playing field”.

- Creating an Orphan Biological Scheme (similar to the Orphan Drug Scheme that is in operation for medicines). In its Human Tissues Review, the Commonwealth Department of Health and Ageing distinguished between human or human-derived tissue and cell products on the basis that cell products “are produced by deliberate alteration of tissue or cells in a defined manufacturing process”\(^{(10)}\).

The NHMRC 2011 discussion paper on the ethics and commercial use of human tissue products introduced the concept of attenuation (a measure of the level of significance placed upon a product derived from human tissue\(^{(11)}\)) as a reasonable basis on which to make decisions regarding commercialisation activities\(^{(11)}\). Perhaps human tissue products that are considered to be minimally attenuated (e.g. where the biological to be transplanted retains significant cellular properties that link the tissue to the donor) can be included in an Orphan Biological Scheme? This would allow eye and tissue banks to provide biologicals used to treat, prevent or diagnose a rare disease, or biologicals that are not commercially viable to supply to treat, prevent or diagnose another disease or condition, to the community without threatening the viability of the eye and tissue banks (thereby reducing community benefit).
Conclusion

The regulation of eye and tissue donation and transplantation by the same organisation that regulates therapeutic goods (pharmaceuticals and medical devices) is unusual internationally. The only examples are Australia and the United States (through the wide ambit of the Food and Drug Administration). Is this approach appropriate, or are other models such as Canada and the European Council and its constituent States (whereby regulation of organs, eye and tissues is undertaken by a Human Tissues Authority or equivalent) more appropriate?

Regulating biologicals as described in the ANZTPA January 2013 discussion paper differs significantly in several key aspects from the draft ANZTPA rules from 2006 prior to the 2007 postponement. Instead they mirror the TGA’s Biologicals Regulatory Framework that came into effect in May 2011 and thus no longer would achieve their stated aim of applying “different levels of pre-market regulation to biological products based on the risks associated with use”. The regulation of biologicals in a joint framework needs to return to its original concepts of risk and levels of pre-market and post-market regulation based on actual assessed risk in the use of the product.

Given the high degree of regulation described relative to the low risks with the use of eye tissue for transplantation, the costs of regulation (direct and indirect) will be unjustifiably high. This includes both a threat to the financial viability of providing the clinical service and to the reduced benefit to the community due to the reduction of available corneas (in the absence of any risk reduction). These threats are most likely to be realised in New Zealand where the existing infrastructure is most vulnerable to inappropriate and unjustified regulatory burden.

Eye banking in Australia and New Zealand must, by law, be non-commercial, not-for-profit undertakings. As such the Australian experience shows that government, through subsidies and payment of direct regulatory fees, has been required to ensure the viability of eye banking and tissue banking services under the current TGA biologicals scheme where a disproportionate percentage of eye bank resources are spent on meeting compliance requirements. Under ANZTPA government support will need to be maintained and increased, and substantial financial support from the New Zealand introduced, to ensure that the donation and transplantation system in Australia and New Zealand is not placed under threat.

Australian experience shows that under the Biologicals Framework as described, product has been withdrawn from the market. Withdrawal is not due to risk of the product but rather a regulatory scheme renders these products non-viable to supply, from both a financial and a compliance point of view. These products are now required to be imported under Special Access Schemes, notionally increasing the risk and demonstrably increasing the cost to the Australian community. An orphan biologicals scheme similar to the Australian orphan drug scheme, and government subsidies similar to the Australian PBS scheme, would have to be introduced in parallel to any biologicals regulatory scheme to ensure equitable access of these tissues to the community.

The ANZTPA consultations of 2006 and 2007 revealed that different standards and requirements would apply on either side of the Tasman (especially in regard to testing services) leading to the possibility of nation specific manufacturing and product licences. Paradoxically this would decrease the ability to share transplant tissue between the nations (including that which is required urgently or in short supply), negating any benefits of a shared regulatory scheme. Standards, requirements and the regulatory approach must be the same on either side of the Tasman. To do this there needs

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to be a re-examination of appropriate levels of regulation related to risk, and in this context examine
the ability of the infrastructure and arrangements on both sides of the Tasman do meet the
regulatory requirements.
References


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