

24/9/2016

To whom it may concern,

Re : Consultation: Regulation of autologous cell and tissue products and proposed consequential changes to the classification of biologicals

Please find below a discussion of a number of areas and questions raised by the TGA in their revised review of the autologous biological therapy regulations.

The revised review has appropriately taken into consideration the submissions to the original review paper and this is reflected in the new options.

The review correctly highlights the problems of current regulation and presents these in a well balanced and accurate way.

It is important to recognize that the current legislation has allowed Australian clinicians and researchers to be involved in world leading translational clinical trials in regenerative medicine. Any change to the legislation must protect this ability and not obstruct Australia's ability to remain at the forefront of medical advancement.

I believe that this review offers the possibility of regulatory change that still encourages translational research and regenerative therapies but within a more scientifically rigorous and safe framework.

I would also like to see further discussion on how other relevant regulatory bodies (ie. AHPRA, the Medical Board of Australia, Medical Colleges) propose to enforce the appropriate behavior of clinicians.

Yours sincerely,



A/Prof Julien Freitag MBBS, BMedSci, FACSEP
Head of Clinical Research
Melbourne Stem Cell Centre

TGA Questions

1. Do you support the proposed approach ?

As both a clinician and researcher in the field of musculoskeletal regenerative medicine I fully endorse the approach taken by the TGA in the new consultation paper. The regulatory problem has been clearly and correctly defined and the objectives of this consultation are appropriate and important in maintaining evidence based medical practice.

2. Do you agree that the proposed options should also apply to registered dental practitioners supervising the autologous use of human cell and tissue products as part of a single course of treatment? Please provide reasons to support this view, or not.

I agree. All practitioners should be required to show an appropriate level of safety in their practice.

3. Please provide your views regarding the proposal to retain the concept of a 'single course of treatment'. Do you consider the storage of autologous cells and tissues as part of a single course of treatment carry risks of such a nature that should require TGA regulatory oversight? Please provide reasons to support this view, or not.

I agree that we should retain the concept of a 'single course of treatment'. Many of the conditions in which stem cell therapies show emerging promise are degenerative long term / lifelong conditions (ie. arthritis). Evidence suggests that in these conditions stem cell therapies may not be curative but offer management options. As stem cell therapies are cost prohibitive, and require autologous donation through surgical harvesting, the ability to store for a 'treatment course' is important.

Storage does introduce risks including sterility, traceability/identification and stability/viability of the tissue/cell. Whilst this remains the responsibility of the medical/dental practitioner it should also meet appropriate Therapeutic Goods Order requirements on storage of autologous products.

4. Do you agree that it is unnecessary to distinguish homologous and non-homologous use in the context of the exclusion (i.e. where the product is also for autologous use, under the supervision of a medical/dental practitioner, as part of a single course of treatment)? Why?

Homologous or non-homologous is an area that is not well defined. Many incorrectly use the terms only in relation to the tissue from which cells are sourced – i.e. if mesenchymal stromal cells were sourced from abdominal fat then injection into the knee would be a non-homologous use. Use of knee joint hoffas fat pad mesenchymal stromal cells would be however homologous and yet the cells share the same mesenchymal characteristics. Further, bone marrow derived MSCs from

the iliac crest would be non-homologous for treatment of knee arthritis though bone marrow MSCs derived from the femoral condyle would be homologous.

If homologous use is clearly defined as **tissues or cells** that form the same basic function and share the same identifiable characteristics then this would be appropriate. Including 'homologous' in the regulation and using this 'tissue and cell' definition may add additional appropriate regulation around how practitioners use cellular therapy.

5. Are any other cell and tissue products currently in use that:

- a. are currently covered by the TG Order; and**
- b. form part of established medical practice; and**
- c. would be more than minimally manipulated (and therefore would be subject to regulation under Options 3 or 4)?**

Options 3 and 4 may impact on hospitals utilising products that involve more than minimal manipulation but are also part of established medical practice. The TGA seeks the views from organisations (and others) on the impacts of this.

I do not believe that Option 3 should severely impact upon the ability of hospitals or clinics to supply autologous products such as cultured keratinocytes and pancreatic islet cells. Option 3 describes regulatory steps that should form part of accepted medical practice. In brief, Option 4 would require hospitals to have GMP accredited facilities and this would not be achievable.

6. Option 1.

Do you support maintaining the current system? Please provide reasons to support this view, or not.

I do not support maintaining the current system. I agree that there theoretically exists appropriate regulations already – AHPRA regulation, Medical Board, Medical Colleges and ACCC – to prevent the unproven and unsafe use of treatments. However there appears to be a lack of action from these bodies in regards to regulation of practitioners practicing outside their area of knowledge and who may be practicing unethically. Unless these regulatory bodies show evidence that they are able to enforce appropriate clinical practice then TGA regulation will need to be amended.

7. Option 2.

Given that advertising a service will still be possible what is your opinion on advertising of autologous cell and tissue products and the impact (including financial impact) of this option on those practitioners currently advertising these products to consumers?

Does this option (Option 2) address the issues presented in this paper?

NB: The financial impact we are interested in includes compliance costs (costs you incur to demonstrate compliance i.e. record keeping and reporting and costs you incur to be compliant with our regulations i.e. purchase and maintenance costs) and delay costs (expenses and loss of income through application and approval delay by the regulator).

I do not believe that Option 2 addresses the issues presented in the paper. Direct to consumer advertising of a 'product' is rare. Advertising a medical 'service' is common place within all fields of medicine.

8. Option 3.

What is the impact (including financial impact) of this option on practitioners currently manufacturing and using these cells and tissues?

To what extent does the requirement to comply with the TG standards increase regulation or whether the manufacture and use currently comply?

Would a requirement to comply with these standards 'add value' in terms of addressing the risks and issues set out in Chapter 2, Part C?

Does this option address the issues? Please provide the reasons why it does or does not.

NB The financial impact we are interested in includes compliance costs (costs you incur to demonstrate compliance i.e. record keeping and reporting and costs you incur to be compliant with our regulations i.e. purchase and maintenance costs) and delay costs (expenses and loss of income through application and approval delay by the regulator).

Option 3 may have considerable impact on practitioners who are currently manufacturing / using autologous cell and tissue therapies. Similar to requirements seen in clinical trials, practitioners will be required to show that manufacturing meets relevant TGA standards and that appropriate outcome data and side effect registries are in place.

Whilst this option has considerable financial and administrative impact upon the practitioner and clinics, I agree with all the requirements. As rigorous manufacturing standards and outcome data including adverse event collection already form part of our clinics routine requirements, this will not significantly impact the way in which we practice.

I believe these additional regulatory standards add significant value in terms of addressing the risks and issues highlighted in this paper.

My concern is that some unproven 'stem cell therapies' may still be assessed as no more than minimal manipulation and will remain unregulated. This needs to be addressed.

Whilst our clinic believes that this option is very achievable and addresses many of the issues of concern within the medical community we would need guidance from TGA in regards to a universal accepted definition of adverse events and how this is to be notified to the TGA etc. Discussion regarding Therapeutic Goods Orders and how they will apply to autologous products would also need to be sought and further clarified.

9. Option 4

What is the impact (including financial impact) of this option, particularly on practitioners currently using these products?

Do you consider that this option address the issues? Please provide the reasons why it does or does not.

NB: The financial impact we are interested in includes compliance costs (costs you incur to demonstrate compliance i.e. record keeping and reporting and costs you incur to be compliant with our regulations i.e. purchase and maintenance costs) and delay costs (expenses and loss of income through application and approval delay by the regulator).

- The impact of this option would mean that treatments utilizing more than minimal manipulation would be classified as Class 2 or greater Biologicals. This would mean TGA would need to be satisfied in regards to quality, safety and efficacy. Production/manufacturing would need to meet formal GMP standards.
- Due to enormous variabilities in processing methods, routes of administration, therapeutic protocols, patient selection, patient autologous variability, disease selection and management it would mean each individual practice and therefore individual practice based cell therapy processing method, treatment protocol etc would need to be independently assessed by the TGA for the above standards.
- The above requirements would be incredibly prohibitive in regards to cost and time. The cost would discourage private entities from investing in ethics approved research and therefore would directly prevent the appropriate clinical development of cell based therapies within Australia.
- This option only serves to discourage appropriate clinical translational research and instead encourage the use of less than minimal manipulation techniques that have no proven level of efficacy or safety.

10. Please provide your views on the proposed new definition of minimal manipulation.

I agree with the new proposed definition of minimal manipulation.

11. Do you support the proposed changes to the classification criteria as set out in the proposed new definitions (to rely on the new definition of minimal manipulation and, as a result, to redefine Classes 3 and 4)?

Yes.

Do you support redefining of the current Class 4 as proposed above?

Yes.

12. Do you consider it is appropriate for the requirements for CTX approval apply to the new redefined Class 3 generally or just to a subset of Class 3 which represent the higher risk biologicals (as well as biologicals coming within the new Class 4 in the future)?

Do you perceive any additional risks in the change for requirements for CTX approval for biologicals in the new redefined Class 3 and Class 4? Should a distinction be maintained for higher risk biologicals in relation to clinical trials and what criteria should this consider? Please provide any information that supports your view.

I consider that a CTX requirement is suitable for that subset of high risk Class 3 as well as biologicals under Class 4. Those biologicals in Class 3 with previous usage history supported by clinical evidence and approved by another national regulatory agency should not require a CTX. Change in the requirement for CTX approval for biologicals may lead to increased costs and create a financial hurdle to some areas of clinical translational research.

Summary

I welcome the revised TGA review of the regulation of autologous cell based therapies.

The areas of concern that have prompted this review have been accurately presented.

Whilst recognizing the strength of the current regulation in promoting translational research and development within Australia, the emergence of unproven, non scientific and potentially unsafe treatments needs to be addressed.

I believe that Option 3 - whilst introducing its own challenges in regards to enforcement and development of clear TGA standards for autologous products – offers the most appropriate regulatory change and importantly still encourages clinical advancement of regenerative therapies within Australia.

Yours sincerely,



A/Prof Julien Freitag MBBS, BMedSci, FACSEP
Head of Clinical Research
Melbourne Stem Cell Centre