Draft submission from NSCFA to TGA consultation on regulation of autologous stem cell therapies

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Preamble: In our view, the basic questions to be addressed are:

1. Are there currently significant risks to patients treated by medical practitioners who claim to be administering autologous stem cells?

2. Can these risks be addressed through a regulatory approach?

Our response is framed roughly along the lines of the questions suggested in the Consultation document.

Q1: What are the public health risks of 'autologous stem cells' in your view?

1. The main risk is a lack of demonstrable efficacy, related to the lack of relevant clinical trial data, or effective documentation of adverse effects, deficiencies directly related to the lack of regulatory oversight, and permitted by, the autologous cellular treatment exclusion under Item 4 q of the Therapeutic Goods (Excluded) Order 1 of 2011.

2. Lack of compliance with standard manufacturing procedures or quality assurance in the preparation of cells to be used as therapeutic agents. Hence the cellular composition of products used is unknown and the cells are uncharacterised.

3. Use of unproven therapies, which potentially deprives patients of access to proven therapies.

4. Participation in unproven non-regulated treatments outside properly constituted clinical trials may make patients ineligible for properly constituted trials in the future.

The following considerations relate to issues of clinical practice and will not be dealt with further in this submission: Significant unreimbursed fees incurred in the use of unproven therapies may reduce patient options to pay gap charges for other more proven therapies; cosmetic doctors and self-styled "stem cell specialists" cannot claim expertise to treat osteoarthritis, Multiple Sclerosis, Parkinson's Disease, autism, cerebral palsy, etc; lack of systematic follow up; products and procedures are advertised and promoted direct to the public.

Q3: What is the evidence for these risks?

1. *Lack of efficacy*: few trials have been done and fewer reported in peer-reviewed literature. Even fewer have shown positive outcomes which would support clinical use.

2. *Lack of follow-up:* Current stem cell businesses do not offer patient medium to long term follow-up or management of post-procedure complications. These are left in other hands, most commonly those of general practitioners who, while competent, do not know what has been done to their patients and have not been trained to deal with subsequent emergent situations. This lack also prevents the gathering of reliable data on adverse effects.

3. *Lack of acceptable manufacturing standards:* Methods of preparation of cells and supernatant solutions are kept secret and are not open to peer scrutiny or the application of the minimum standards applying to all other therapeutic products. The administered product is undefined.

Q4: What identified risks should have the highest priority for resolving?

1. Lack of clinical trial evidence
2. Lack of assessable manufacturing standards and hence, of confirmed product integrity
3. Lack of patient follow-up and accurate inventory of adverse effects

Q5: Are there public health benefits, such as patient access to new and novel treatments, to consider?

1. No, since there are virtually no peer-reviewed positive clinical trial data and none that validate current commercial practice.

2. Clinical trials to underpin commercially available treatments would/should be carried out in academic/ teaching hospital environments, where there are staff trained in research methodology, facilities for recording individual patient data and progress, and subsequent statistical analysis.

3. Very few properly constituted trials are being performed, and "Patient Registries" mentioned on practitioners' and Regeneus's websites are not a substitute. The present 4q exclusion order facilitates this and acts against proper clinical development via the trial process.

Q6: What do you see as the likely risks, benefits and costs of each option to you? If possible, please attempt to quantify these costs and benefits.

Option 1: Continue to exclude autologous stem cells from regulation under the Therapeutic Goods Act 1989 (the Act)
Response: We do not support this for the reasons stated above

Option 2: Exclude autologous stem cells from regulation under the Act in defined circumstances

Response: No. The products used are (probably) more than minimally manipulated and generally not for homologous use. We know very little about the nature of the cells and supernatants being administered and this option does not address the issues of manufacture, safety, efficacy or adverse event monitoring.

Option 3: Regulate autologous stem cells under the Act, but exempt from registration and manufacturing requirements
Response: No, the products (and doctors) need to be safe and efficacious

Option 4: Regulate under the Act as Class 1 biologicals
Response: No, not homologous or minimally manipulated

Option 5: Regulate under the Act as Class 2, Class 3 or Class 4 biologicals
Response: yes: other forms of cell therapy went through extensive evaluation in the academic/teaching hospital environment with extensive publication and peer review. This should equally apply to these newer forms of cell therapy. Practitioners should be under scrutiny and therapy evaluation should meet the minimum criteria of HREC approval and informed patient consent.

Q7: How do you think each option addresses the risks you identified in the earlier question?

Critical to the evaluation of the 5 options for 'regulation of autologous cells' presented in the table on p. 8 of the consultation document, are the following:

i) In the Overview and Scope section of the Consultation Document, it is stated that currently exempted autologous tissue and cellular product use as per Attachment 1, are not the subject of this discussion and therefore presumably NOT intended to be included in the considerations of options 1-5. In some sections of the document however, reference is made to 'autologous stem cells', in others only to 'autologous cells'.

ii) if the currently excluded tissues (other than non haemopoietic autologous SC) are NOT under consideration, then the majority of current commercial 'stem cell' products\ may be more than 'minimally manipulated' particularly if stem cell expansion in culture occurs, though it is difficult to assess given the lack of available detail re manufacturing processes. Homologous use, as defined, would also appear to be uncommon (given that the majority of current 'stem cell therapies' are adipose tissue derived cell mixtures that are injected into joints or IV, not sites of normal adipose cell function). Cellular products intended for homologous use are likely to be more than minimally manipulated (ie CAR 'T' cells for immunotherapy post BMT) These products would then de facto be regulated as Class 2,3,or 4 biologicals whether the over-riding regulation were option 2 or 3.

Option 1: Continue to exclude autologous cells from regulation under the Therapeutic Goods Act 1989 (the Act)
Response: Doesn't address the risks at all

Option 2: Exclude autologous stem cells from regulation under the Act in defined circumstances

Response: Would not apply to the majority of products in commercial use and doesn't address the risks regarding safety, adverse event reporting and efficacy nor address the questions around manufacture and cell characterisation.

Option 3: Regulate autologous stem cells under the Act (but only minimally manipulated, for homologous use), but exempt from inclusion on the ARTG and manufacturing requirements
Response: Doesn't address product specification, safety or efficacy but would collect adverse effect information.

Option 4: Regulate under the Act as Class 1 biologicals
Response: It is difficult to envisage that these products could be declared Class 1 Biologicals as the classification is envisaged to accommodate biologicals of low public health risk with **high individual benefit,** which has not been demonstrated. This option would evade the critical issues of safety and efficacy.

Option 5: Regulate under the Act as Class 2, Class 3 or Class 4 biologicals
Response: preferred option, requires an evidence base, proper clinical development processes

Q8: Are there additional issues with the regulation of autologous stem cells that any changes should consider and/or address?

1. lack of a scientific basis for clinical use
2. lack of clinical trial evidence for safety and efficacy
3. Lack of standards for manufacturing equivalent to GMP for pharmaceuticals and biological products

It would be important to ensure that a move toward regulation of unproven autologous stem cell therapies does not inadvertently negatively impact on the use of any of the clinical autologous procedures/ treatments as listed in Attachment 1.

Further Comment: Since Stem Cell Treatment Companies provide no information regarding preparation processes, it is not possible to gauge the extent to which cells are manipulated prior to re-injection or, indeed whether they are likely to survive preparation at all. Any kind of cell passaging appears to us to go beyond any of the international standards for "minimal manipulation" that the Consultation Document describes in Attachment 3.

Q9: Is there an argument that autologous stem cells are not therapeutic goods and, therefore, should remain under the current Section 7 declaration?

Response: No

Q10: Should autologous stem cells that are more than minimally manipulated and/or are not for homologous use continue to be excluded from regulation?

Response: No

If you answered 'Yes' or 'No', please provide further information about your response:

1. As acknowledged in the Discussion paper and in the Biological Classification, the greater the degree of cellular manipulation, the greater the risk of the product itself being non compliant with one or more of the manufacturing specifications. Non homologous use introduces additional risks related not only to potential aberrant cellular differentiation but also related to the mode / site of delivery, making it imperative that adequate safety and efficacy data are obtained allowing risk- benefit evaluation of the therapy overall.

2. Regulatory oversight of product manufacturing (as per option 5) would ensure compliance with applicable Standards and give greater confidence in the product being administered.

3. Well designed clinical trials should gather safety data with respect to product administration and efficacy in different disease states, both in the short and longer term. Given that this data is required for listing on the ARTG and for marketing of the product there will be an incentive for the design and support of trials by industry.

4. While relatively few adverse events after autologous cell therapy have been reported, life threatening events such as pulmonary embolism after adipose derived MSC injected intravenously, make it imperative that patients have therapy under the supervision of specialists experienced in cellular therapy and its potential complications, until safety data is well documented.

Can these problems be addressed within a regulatory framework?:
Among other possibilities, we wish to draw the Authority's attention to practitioners' common claims that these treatments are in the nature of clinical trials. Many of the issues we identify could be addressed through obligations to register such "trials" under the Authority's CTX scheme, with protocol assessment by designated HRE Committees and pharmacovigilance-type protocols over relevant time bases, say 2 years. This would provide data relating to efficacy and adverse effects without infringing on the sensitive issues of individual practice or commercial priorities.