COUNCIL OF EUROPE CONSEIL DE L'EUROPE

SP-CIT(2004)1

Council of Europe

Comments on the project of a European Regulation on human tissue engineered products

The Commission, DG Enterprise, has circulated a consultation paper and organised a meeting of experts in Brussels on 29 April 2004 on the subject of harmonised regulatory framework on human tissue engineered products.

The main justification for a Regulation seems to be the wish of the industries for a community legislation, based on the EC Treaty Article 95 rather than Article 152, for products which may neither be regarded as medicinal products or medical devices, nor as products covered by the regulations of the directive on safety of tissues and cells (2004/23/EC).

1. The main difficulty regards the field of *tissue engineering* in relation to the fields of *medicinal products* and *tissues and cells.*

- While the Directive 2004/23EC of 31 March 2004 on tissues and cells applies for the donation, procurement and testing of tissue and cells intended for engineering purposes, other European legislation may apply for the processing, preservation, storage and distribution.
- The Commission Directive 2003/68/EC, modifying Directive 2001/83/on the Community code relating to medicinal products for human use, Annex I, Part IV.2, applies for : medicinal products for somatic cellular therapy. Such products may be of autologous or allogeneic origin. The biological characteristics have been clearly modified and the effects occurs through metabolic, pharmacological and immunological means. This manipulation includes expansion or activation of ex-vivo cellular autologous populations, utilisation of allogeneic cells associated with medical devices, utilised ex-vivo or in-vivo.

  - This definition is very broad and may potentially include many of those cells that the tissues and cells directive was created to cover. Now, many of these cells may also fall under the proposed regulation on tissue engineering.

  - This definition, taking into account the type of action, is a transposition of the distinction existing between medicinal products and medical devices. Unfortunately, this distinction is not discriminating for living cells, all of which may pertain to one or several of these effects.

- Today many academic centres are involved in clinical trials with several new cellular therapies, such as:

- Stem cell derived progenitors for blood as well as for other tissues
- Monocyte derived dendritic cell (DC) vaccines and tolerogenic DCs or T cell derived cytotoxic cells against tumour cells or viruses
- Olfactory Bulb Nervous Tissue transplantation in injured spinal cord to correct paraplegic patients

- All these regenerative/corrective cell therapies basically need purification, culturing, expansion of cells and coincide mostly with a more or less drastic phenotypic change of the involved cells. The mentioned therapies, however, mostly do not involve co-transplanted matrices/carriers or scaffolds. The majority of these products moreover, are single use preparations for a single- often autologous-patient/recipient. A clear call for general adaptation of GMP like procedures for these highly complicated products is apparent from several Council of Europe and EU reports and recommendations.

- The TEP concept report in this respect seems erroneously to involve all the above-mentioned products. This ambiguity has to be avoided while pharmaceutical batch wise clearance for these products is mostly impossible because of the intrinsic patient-to-patient variability, further the need for immediately use hampers extensive testing. Therefore products such as the above mentioned "cell only" products should clearly be separated from the TEP reports scope and influence.

– The project on tissue engineering would apply to products substantially manipulated (affecting physiological function), with properties of a regeneration, repair or replacement of tissues and human cells, as long as new tissues are structurally and functionally analogous. These tissues are derived from living cells and tissues, whether the final product is viable or not. They may finally contain cells, biomolecules or biomaterials.

- The notion of regeneration, repairing or replacing potential opens an extremely wide field. There too, the processing of haematopoietic cells could very well be dependant not only by the proposed Regulation, but also on regulations in the different directives, a situation which would not add value but rather cause confusion.

- The notion of structurally and functionally analogous tissues further complicates the situation: cartilage utilised for repairing could also enter the field of the directives and the proposed Regulation. If utilised, however, to treat bladder incontinence it does not belong to the field of tissue engineering anymore, but to one of the two other directives.

- The above-mentioned cellular variability and testability also holds true for cells combined with engineered materials (matrices and scaffolds). Therefore, again, the cellular components should be exempt from the medicinal-product-like certification.

2. The non-remunerated donation principle, as defined by the Council of Europe, should be adhered to. Thus, all cells and tissues should be clearly left out from commercialisation. Only non cellular components of TEP and the services should be allowed for

commercialisation, otherwise it could create serious public opinion problems in the willingness to donate.

3. Ethical issues also have to be considered: the patients will not understand why the TEP report views the patients' cells prepared from and for him/herself as a "Commercial Product" because of the EU legislation.

4. The authorisation procedures proposed constitute another point of discussion. It is proposed that autografts should be managed by a national authorisation procedure with the possibility of an optional centralised procedure (EMEA) for industries, and a centralised authorisation procedure for allografts with a possibility of derogation for a single case use, which would be managed at the national level.

Autologous and allogeneic products for single-case use, processed by non-commercial academic institutes, due to their varying composition and design, should not be subject to a product authorisation procedure. Rather, the there should be a procedure for authorisation/licensing/accreditation of the institute performing the processing. In the case of autologous use, which might be regarded as mainly hospital care, the EC Treaty Article 152, 5th paragraph should be respected.

It is difficult to decide on an authorisation procedure as long as the nature of products concerned by the proposed Regulation is not known. In practice, it would probably be much easier to elaborate a text adding to the Annex I, Part IV, of the Directive 2003/63/EC a centralised authorisation procedure for what would be considered as tissue engineering, and particularly the combination with biomaterials (medical devices). For allogeneic products with serial risk, a more logical solution would be to consider them as medicinal products and utilised authorisation procedures already established.

Conclusion

The proposed regulatory framework deals with issues that cross the boundary between cellular and medicinal products. Thus, its scope is not and cannot be quite clear. The proposed procedures for authorisation of engineered tissue and cell products, although well motivated for commercialisation of industrial engineered products, may seriously hamper further development of many products, especially those intended for autologous and single-case allogeneic use.

Furthermore, the TEP report justification of enhancing the safety of patients treated with TEP is not served by erecting new licensing barriers for also the cellular components while for the used matrices and scaffolds, adherence to safety regulations for medical devices will suffice.

If the industry needs/request more regulation for tissue and cell products (engineered or not) it would probably be a better approach to add annexes for commercial cell and tissue products to the already existing Commission Directive 2003/63/EC. In this way both routine and newer therapeutic small scale treatment options within the non-profit seeking academic world could continue to develop within frames that are more relevant for its purpose. Not to loose one of the main ideas on the tissue engineering product regulation, the tissue, cells and the medicinal product directives could then also be modified to include products, which are currently not entirely included in any of them. The result would then hopefully be two directives meeting all the needs, rather than three regulatory systems that might cause inefficiency due to

confusion and furthermore could hamper future development due to the problems which appear when the same rules are set for products processed by non-commercial academic institutions as for products processed by commercial companies.