EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

June 2002

" Consultation document"

Need for a legislative framework for Human tissue engineering and tissue-engineered products

1. Human tissue engineering and tissue-engineered products

Tissue engineering is a new and rapidly developing technology whose aim is to produce viable substitutes that restore, maintain or improve the function of human tissues or organs. It differs from standard therapies by the fact that the engineered products become integrated within the patient, affording a potentially permanent and specific cure of the disease, injury or impairment. It is an interdisciplinary field that applies the principles of biology and engineering.

Typical examples of tissue-engineered products are orthopaedic prostheses (bones), cardio-vascular prostheses (heart valves, blood vessels, arteries), neurological tissue repair, skin repair, muscle repair, liver or pancreas regeneration or prosthesis, prosthesis for urinary tract.

The potential market world-wide for tissue-engineered products is estimated by the Pittsburgh Tissue Engineering Initiative at nearly €100 billion per year.

2. Patient protection and public health

Tissue engineering is far from having reached the maturity and the stability of the pharmaceutical or medical devices sector, and neither the development of knowledge and technologies nor the potential risks are fully foreseeable.

The challenge for the legislators, therefore, is to strike the correct balance between the possibility for patients to gain rapid access to new and highly promising types of products, and appropriate guarantees on safety and quality.

3. The need for an appropriate Community legislative framework.

There are various reasons why tissue engineering and tissue-engineered products could be covered by an appropriate Community legal framework.

- Due to the high complexity, variability and permanent evolution of living cells and tissues, as well as the complexity of their processing, it is difficult to estimate the risks relating to such products. However, the potential benefits for the patient are very high. A legislative framework could therefore be developed allowing patients to take the full benefit of technological evolution, whilst maintaining the highest levels of safety.

- In the absence of a European legislative framework, Member States have started to implement policies at the national level. As these differ from one Member State to another, patients' access to such products may not be ensured throughout the Community. The goal of any directive should be to achieve access of tissue engineered products to the whole Community market and to increase trust in products irrespective of origin.

- From an industrial policy point of view, the Community needs to provide the increasing number of companies involved in tissue engineering with a clear and transparent legal framework, in order to create the legal certainty needed to protect their investments and activities, and offer European citizens access to this new technology.

Different opinions have been expressed as to the scope of any legislation for tissue engineering.

As indicated by the Commission's Scientific Committee on Medicinal Products and Medical Devices[1], some tissue-engineered products may be considered analogous to medical devices, but in many ways they are quite different. Similarly, some carry risks of the same types as are associated with pharmaceuticals (cell therapy products), but again are very different in other respects. It therefore concludes that there could be a need for a specific legal framework, different from the medical devices and pharmaceutical products regulatory systems.

Another possibility might be to include a tissue engineering legislation in one of the existing legislative frameworks (Pharmaceutical or medical devices).

Question:

1. *Is the Committee's suggestion for a new specific legal framework, different from the medical devices and pharmaceutical products regulatory systems, the preferred option? Should there be a differentiated approach between different kind of products?*

4. Definition and Scope

As yet, there is no agreed definition of tissue engineering. The Scientific Committee suggests that tissue engineering is the "regeneration of biological tissue through the use of cells, with the aid of supporting structures and/or biomolecules". However, as the Committee states, there is a need to produce a scientifically valid and legally sustainable definition of tissue engineering, and tissue-engineered products, in order to underpin a legislative framework and to provide a sound basis for demarcation between tissue-engineered products on the one hand and medical devices, pharmaceutical products and cell therapy on the other.

According to the Scientific Committee, a medical technique should not be regarded as tissue engineering when it involves the isolation of cells from some appropriate donor and their delivery to the site of treatment with only minimal manipulation.

In this context, attention is drawn to two documents influencing the present consultation:

- A proposal for a Directive concerning the donation, procurement, testing, processing, storage and distribution of human tissues and cells. This proposal concerns mainly the question of sourcing and transplantation.
  Among other things, this directive will cover the selection of donors, procurement and testing of the tissues to be used for the production of engineered tissue.

- A web-consultation concerning a modification of Annex I of Directive 2001/83/EC on medicinal products, which concerns inter alia the contents of the dossier for marketing authorisation for human or animal somatic cell therapy medicinal products.

In the light of these two documents, the framework envisaged will exclude gene therapy and would relate to human organs produced by a process of bioengineering (BioOrgans), tissues and cells,

[1] Opinion of the State of the Art concerning tissue engineering, October 1, 2001.

autologous and allogeneic, both non-viable and viable, and including combined tissue/non-tissue type products that have been substantially modified by treatments, and that do not exert their effect through metabolic, pharmacological or immunological means.

It is proposed not to cover xenogenic organs, tissues and cells as they are considered to be already covered by the medicinal product directives.

Questions:

2. *Is the idea to cover "human BioOrgans, tissues and cells, autologous and allogeneic, both non-viable and viable, and including combined tissue/non-tissue type products that have been substantially modified by treatments, and that do not exert their effect through metabolic, pharmacological or immunological means" an acceptable basis for a legislative scheme?*

3. *Would there be a need, in case a specific legal framework has to be set up, to reconsider the scope of existing legal provisions (for Medical devices, Medicinal products or others)?*

4. *How should borderlines be defined, for instance regarding cell therapy or stemcells? Would the fact that cells have a metabolic pharmacological or immunological effect be the only criteria relevant for legislative purposes?*

5. *Should xenogenic organs, tissues and cells be partly covered in the directive, why and how?*

5. Outline for a possible Community legal framework

The framework would need to cover in an efficient and flexible way the whole process, from company, production process, handling, storage, transport, up to traceability of the donor.

The main elements to achieve a balance between access to new technologies and protection of health appear to be the following:

Performance-based requirements: products should under normal foreseeable conditions achieve their intended purpose with demonstrated performance/efficacy.

Risk management approach: the placing on the market and use of products should be based on a risk analysis and risk management approach and a risk/benefit analysis.

Need for more detailed rules: as the legislative framework may have to be limited to fundamental issues in order to allow for technological progress, there is a need for instruments to provide further, detailed rules in relation to specific aspects. These may take the form of:

- Guidance documents compiled by authorities;
- Binding rules adopted by authorities;
- Standards for voluntary application, compiled by the relevant European standards bodies (e.g. for the matrix).

It appears essential that, whatever legal form they take, such detailed rules remain coherent in relation to the whole area of tissue engineering, covered, as it may be, by different legal instruments.

Appropriate mechanisms will have to be adopted regarding issues such as **clinical data, traceability of donors and patients**, **vigilance**, with mechanisms allowing authorities to **intervene on the market** where health issues do or are likely to occur.

Questions:

6. *Is there a role for European standards in support of a future legislative scheme, for instance regarding quality assurance?*

7. *Would guidance documents in support of a future legislative scheme have to be developed by authorities?*

8. *Is there a potential need for complementary binding specifications, adopted by the Commission in co-operation with Member States?*

9. *Are these instruments mutually exclusive, or can one envisage them being applied to different and distinct aspects?*

10. *Are the provisions on clinical tests for new biological medicinal products (approval to start the clinical trials) appropriate?*

6. Authorisation and market access

Basically, a decision has to be taken regarding the conditions under which products can be placed on the market. Whilst it seems clear that market access should be subject to prior authorisation, various mechanisms might be envisaged, inspired by the directives on medicinal products and medical devices, in relation to mechanisms:

- One possibility is to base these conditions on a two-stage approval system, distinguishing between the licensing of the production plant, and market approval of the product.

- Another possibility is an integrated quality system, in which the market access of products would be based on the company's quality system in relation to specific products and a specific assessment of that particular product.

Questions*:*

12. *Are the two approaches mutually exclusive?*

13*. Which one is to be preferred from the safety and policy point of view?*

7. Procedural aspects of the evaluation process

One of the major concerns for public authorities in the assessment of tissue-engineered products is the scarcity of resources possessing the necessary expertise, and the need to have full confidence in assessment activities conducted in other Member States.

For these reasons, whatever procedure leading to market access should be based on full transparency throughout the process. Various options exist:

- An application for market access would be submitted to a national authority, which would have responsibility for approving the product. The examination of the application would however, if necessary, be carried out in co-operation with the authorities of other Member States. The national authority would prepare a draft, to be submitted to an advisory committee made up of representatives of Member States. The opinion of this committee would be sufficiently authoritative for the national authority to whom the application was introduced to accept it as a basis for its decision providing access to the Community market.

  It might also be the case that under such a system the national authorities each take a decision on national market access on the basis of the opinion of the Committee.

- Under a more centralised procedure, the application would be submitted to a central body/authority responsible for both evaluation and approval. This central body would be composed of representatives of Member States with appropriate expertise, who would determine the conditions under which the assessment of the application is to be carried out and formulate the conditions under which market access is granted. Decisions on market access would have to be taken by the Commission in conformity with the Member States' opinion.

  Under such a system, it is possible to give responsibility for procedural aspects to an Agency. This could be the EMEA.

- The Scientific Committee has suggested that a European Tissue Engineering Regulatory Body be created to supervise the introduction of tissue-engineered products and monitor them.

Questions:

14. *Is one of the options set out to be preferred?*

15. *If an agency becomes involved, should a separate agency be created, or could the competencies of EMEA be extended?*

INVITATION TO COMMENT ON THIS PROPOSAL : YOUR CONTRIBUTION

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DOCUMENTS AVAILABLE:

◆ ***Documents of the Commission:***
- Commission proposal for a Directive on setting standards of quality and safety for the donation, procurement, testing processing, storage, and distribution of human tissues and cells.
  http:// as soon as possible……
- Directive on medical devices
  http://europa.eu.int/comm/enterprise/medical_devices/communitywidelegalframework.htm
- Amendment of Directive 2001/83 of medicinal products Annex 1
  http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2002/april/2001_83_an1.pdf

◆ ***Opinion of Scientific Committee on Medicinal Products and Medical Devices on the State of the Art concerning tissue engineering, 1 October 2001***
http://europa.eu.int/comm/food/fs/sc/scmp/out37_en.pdf

◆ ***Document communicated to the Commission:***
United Kingdom
- A Code of Practice for the Production of Human-derived Therapeutic Products
  http://www.medical-devices.gov.uk

◆ ***USA legislation*** :
http://www.fda.gov/cber/rules/frtisreg011901.pdf
http://www.fda.gov/cber/rules/gtp010801pr.pdf
http://www.fda.gov/cber/rules/suitdonor.pdf

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