The European Commission
Enterprise Directorate-General
Unit F3 – Biotechnology, Competitiveness in pharmaceuticals, cosmetics
B-1049 BRUSSELS
E-mail address: entr-human-tissue@cec.eu.int

April 29, 2004

Dear madam, sir,

The Dutch Forum for Biotechnology and Genetics (FBG) is pleased to hereby submit its views on the Proposal for a harmonised regulatory framework for human tissue engineered products – DG Enterprise Consultation Paper.

A total of 42 organizations affiliated with the FBG are active in the fields of medical biotechnology and human genetics. The FBG comprises patient associations, health care providers, health insurance organizations, sc ientists, and (the pharmaceutical) industry.
The FBG perceives its primary objectives to be the identification of new developments in the field of medical biotechnology and human genetics, and to encourage developments which offer an added value to health care. The FBG aims to serve as a forum, i.e. an extensive network of participants who are offered an opportunity by the Forum to inform each other, at an early stage, of new developments and of national and international policies pertaining to those develo pments.
The FBG also assesses new developments in terms of their contribution to the improvement of health care and public health. The members' contributions provide information of importance to the preparation of definition reports and issue papers for th e authorities and politicians at both national and international level. These are intended to contribute to balanced communications, opinion-forming and decision-making by the national government, politicians, and other organizations involved.

Pursuant to this objective the FBG would welcome an opportunity to make a contribution to the regulations for human tissue engineered products you are currently developing at a European level. In preparing its response the FBG has endeavoured to adopt a problem-oriented approach, rather than create problems which do not exist; to base its deliberations on existing structures; and to seek solutions that will not impede scientific research, and which will consequently encourage innovation.

The FBG wishes to submit the following comments, which are accompanied by a number of considerations and recommendations:

1. Pursuant to the European regulations (Directive 2004/23/EC) the procurement of tissue and cells is based on the principle of voluntary and unpaid donations. Howev er, the FBG observes that this Directive does not exclude the possibility of commercial institutions storing human tissues.

   The FBG is divided in its opinion as to whether commercial storage should be excluded. A majority of its members are of the opini on that commercial storage should be permitted, provided that the donor receives transparent information. However some members are of the opinion that the storage of tissue which is not used for innovative purposes and which is not protected by patents sho uld be a public matter analogous to the donation of blood.
   For consideration: the FBG requests the EU to ensure that, within the scope of the informed consent procedure, donors receive information about the fact that the EU conducts a policy

which strongly discourages the procurement of tissue and cells for profit motives.

2. The FBG notes that it is impossible to make an explicit distinction between engineered and non-engineered human tissue, an inability which is due to the absence of a generally applicable definition of non/marginally-engineered and engineered human tissue. The difficulty in establishing such a definition is also apparent from the many discussions on the issue, both in Europe and the rest of the world.
   Nevertheless, it is the FBG's view that the specification of the demarcation within the definition of human tissue engineered products should serve as the underlying principle.
   For consideration: The FBG has endeavoured to arrive at a practical definition.
   Engineering is an issue in the event of:
   1. manipulations which influence the physiological function of a cell population and/or
   2. manipulations of a cell population which result in changes in the composition of the cell population, inclusive of procedures such as depletion and selection procedures.

   Consequently the term 'non-engineered' is used in connection with manipulations which are focused exclusively on storage or cryopreservation, and which do not result in changes to the composition of the population and are not intended to exert an influence on the function. Consequently pursuant to this definition of 'non-engineered' manipulations extends both to the reduction of the volume and the addition of a cryoprotective agent.
   Recommendation: The preparation of a list in the new EU regulations which specifies which manipulations, pursuant to the above definition, are regarded as resulting in 'non-engineered' products. This list could also include manipulations which, pursuant to the above definition, are regarded as resulting in 'engineered' products but nevertheless deemed to be exceptions, based on an estimation of the risks. Consideration could be given to manipulations which have become generally-accepted practice and have not been found to cause problems. This list would need to be kept up to date, and amended where necessary.

3. The FBG is of the opinion that it is possible to define requirements for human tissue engineered products on the basis of the existing EU medicines legislation. This would need to be based on a detailed study of what is and is not applicable to tissues. This study could be carried out by a European committee of experts.

4. The FBG is of the opinion that a regulatory framework will need to be developed for the assessment of human tissue engineered products. The FBG wishes to emphasise that account will need to be taken of the specific characteristics of this category of products. For example, it is difficult to carry out dose-response studies and quality-control tests on these products; moreover occasionally the reproducibility of the manufacturing process will depend on the source tissue. It is highly unlikely that large numbers of human tissue engineered products will be launched on the market in the forthcoming years. Consequently during this periodic will be necessary to develop the necessary knowledge and experience. However, this should not result in procedural uncertainties or frequent modifications of the regulatory framework, since these would result in innovative companies suffering from excessive delays.
   For consideration: The FBG requests the EU to give consideration to the formulation of the criteria at a European level, since an adequate amount of necessary expertise will only be available at this level.
   Recommendation: The manipulation processes required for both autologous and allogenic products will expose patients receiving these products to the same risks, and consequently both categories of products should also be governed by the same criteria. In addition, in view of the nature of the products preference is given to process evaluations rather than product evaluations.
   Recommendation: The assessment framework should be formulated on the basis of controlled risks. This will require flexibility, transparency, collaboration with the stakeholders, and dynamic action.

5. The FBG is of the opinion that it is currently difficult to organize clinical trials for human tissue engineered products. It should be realised that the current assessment criteria applicable to

clinical trials rely on evidence-based criteria, and pertain to the creation of an adequate statistical basis by means of e.g. double-blind techniques and the size of the group. This is not feasible for clinical trials with human tissue engineered products, as they can pertain to small-scale trials which are often carried out by a specific institution.

Recommendation: The small numbers of patients who come into consideration for scientific clinical tests with tissue engineered products could give cause to the adoption of a methodology analogous to that employed for orphan drugs.

6. Another issue which the FBG considers to be of importance pertains to the requirements that will need to be imposed on the designated agency or institution assigned the responsibility for the acceptance of human tissue engineered products. This acceptance could be comprised of an accreditation and/or a dossier assessment of the product/process control. To avoid discrepancies the acceptances will have to meet the criteria governing non-engineered tissue, supplemented by additional requirements.

7. The FBG's view is that, in general, excessively-stringent requirements for acceptance will ultimately prevent companies from achieving returns from their development programmes. This will impede the development of products of this nature, a situation which will also be detrimental to the patients.

   Recommendation: In the FBG's opinion the assessment of the safety and quality of each product should be based on a risk-management programme. This would require institutions to adopt a responsible approach to in-house analyses of the risks and, where relevant, the implementation of measures to restrict those risks.

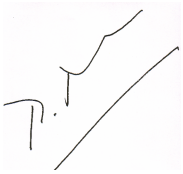
In summary the FBG wishes to submit the following recommendations:

- The preparation of a dynamic list of manipulations which, pursuant to European legislation, are regarded as resulting in 'non-engineered' products.
- The same assessment criteria should be employed for both autologous and allogenic products.
- Preference is given to process evaluations rather than product evaluations.
- The regulatory framework for human tissue engineered products should not be amended too frequently, and should not result in procedural uncertainties. This would cause delays, rather than encourage innovation.
- Preference is given to the design of clinical trials which employ an approach analogous to that adopted for orphan drugs.

- To avoid discrepancies the acceptance of institutions working with non-engineered products should go hand in hand with the acceptance of and criteria for human tissue engineered products.
- Assessments of the safety and quality of products should be based on the requisite risk-management programme.

We trust that the above answers shall provide sufficient impetus for the further development of policy at a European level, and remain

Yours sincerely,
The Chairman of the Forum Biotechnology and Genetics,



Dick Dees