Joint industry comments on

PROPOSAL FOR A HARMONISED REGULATORY FRAMEWORK ON HUMAN TISSUE ENGINEERED PRODUCTS:

DG ENTERPRISE CONSULTATION PAPER*

13 August 2004

Contribution of the biotechnology industry to the draft regulation of the European Commission for Human Tissue Engineered Products (hTEPs), following the 16/04/2004 Multi-Stakeholder meeting organised by DG Enterprise and the 23/06/2004 meeting of Commission members with the EuropaBio/Eucomed/EBE Expert group

The enclosed document is aiming at providing the European Commission with supplementary ideas/proposals concerning the following aspects of the draft regulation:

This document is a follow-up to the joint industry position paper which was addressed to the Commission on 30/04/2004 following the public consultation and stakeholder meeting of 16/04/2004
http://www.europabio.org/positions/Posengineering.doc

1. Scope

1.1. Viable & non-viable cells and tissues

The industry was advised that the Commission is proposing that an hTEP final product must contain living (viable) cells.

The view of the industry is that the proposed new Regulation should cover both viable and non-viable cells and tissues.

Concern has been expressed that there is a risk that non-viable cells and tissues may remain unregulated for an extended period. This will be to the disadvantage of the research industry and patients.

In the event that the Commission is unable to include both viable and non-viable cells and tissues under the same Regulation, it is envisaged that non-viable cells and tissues could be regulated as medical devices following amendment of the Medical Devices Directive 93/42/EEC. Such an amendment, however, would be subject to agreement on this and other aspects of the review of the Medical Devices Directive and it could mean an indeterminate period of non- regulation for non-viable cells and tissues.

In addition, for non viable products currently under development, that are derived from human tissue and have tissue regenerative properties, it is most appropriate that they be regulated under the new proposed Regulation.

For these reasons, the industry asks the Commission to reconsider their position so that the scope of the proposed regulation covers both viable and non-viable tissues/cells.

1.2. Material of animal origin

There is general agreement that the new hTEP Regulation should not -- at least not in the first phase -- cover xenogeneic tissue engineered products. This should be clearly reflected in the provisions defining the scope of the new Regulation. At the same time, however, adequate care should be taken not to exclude human tissue engineered products for which certain manufacturing steps also involve the use of viable material of animal origin. For instance, hTEPs can be made using cells of animal origin [e.g. murine 3T3 fibroblasts for keratinocyte culture]. In fact, many hTEPs are produced using some viable animal material during the production and have a long history of safety. These materials of animal origin do not, however, perform any function in the finished product, in which they are not intentionally present but the presence of small quantities or traces cannot be excluded.

Obviously, non-viable material of animal origin can also be intentionally present in an hTEP. However, the presence of non-viable material of animal origin in the manufacturing process of hTEPs, such as it is for medicinal products or medical devices, does not classify them as xenogeneic (e.g. see definition in Directive 2003/32/EC). For instance, a matrix composed of or containing bovine collagen, horse collagen or hyaluronic acid for rooster combs may perform a structural function in an hTEP, or reagents of animal origin are used in the preparation of culture mediums.

In addition, there is agreement that the combination of medical devices and HTEP will be covered by the hTEP Regulation, whereby the medical device part, without necessarily

needing to be CE marked, shall be tested in the evaluation procedure in accordance with the methods contained in the Medical Device Directive. In this case, a matrix - being of animal origin and rended non viable – that is performing a structural function in the final hTEP must be considered as a medical device and shall conform to the requirements of 93/42/EEC and 2003/32/EC.

The safety considerations related to the manufacturing processes involving viable animal material and the processes rendering animal material non-viable* will have to be reflected in the authorisation procedure as well as in the requirements relating to infection and microbial contamination.

** Reference could possibly be made to guidance documents e.g. in the medical devices sector MedDev 2.5/8 rev2 and Directive 2003/32.*

Provisions on the scope

Depending on the wording of the definition of hTEPs and of the scope of the draft new Regulation, the following legal text can be used to address the above mentioned considerations:

(i) By means of exclusion of xenogeneic products:

- Provide that the hTEP Regulation does not apply to xenogeneic products.
- Use the following definition:

  "Xenogeneic products are, for the purposes of this Regulation, products that intentionally contain viable materials of (non human) animal origin to perform a function in the finished product."

(ii) By means of specification of the hTEP concept:

- Include the following:

  "During the manipulation of the human cells or tissues materials of animal origin can also be used to achieve the desired physiological functions, provided that no material of (non-human) animal origin performs any function in the finished product."

  Or

  "hTEPs containing not intentionally small quantities or traces of material of animal origin (used during the manufacturing process) which do not perform any function in the finished product are not, for the purpose of this regulation, regarded as xenogenic products."

Review procedures

The use of any material of animal origin in the preparation of an hTEP will be reviewed specifically under the assessment of the application for a marketing authorisation, as well as in the requirements relating to infection and microbial contamination, for risks of transmission of infections and on the appropriate techniques for rendering material non-viable.

1.3. Single use/single patient

Products which have not been submitted to a formal pre-clinical and clinical development process and/or for which solid and scientifically defendable safety and efficacy data have not been collected are experimental treatments and need to be handled according to the principles and legislation which exist for investigational TEPs and clinical trials for TEPs.

The following definition is proposed:

'A single use hTEP is represented by a specific single transfer of cells on a 'one-off' basis using a unique process from one patient to the same patient and which is compatible with the clinical needs of that patient.

This single transfer of cells will not follow a standardised procedure. However, it must be compliant with the quality standards applicable to hTEPs. 'Such products fall outside the scope of the marketing authorization process. Patients must be informed of the status of such products and declare an explicit informed consent to the treatment.**Error! Unknown document property name.**

We also believe that a special regime should be applicable to those products, which, depending on the very specific physical characteristics of a named patient (for example, allergies to specific materials generally used in the manufacturing of these products), cannot be manufactured according to standard approved procedures. These products, which shall be limited to be used on a specifically named patient, probably only once, shall nevertheless be accompanied by a document, issued by the prescribing physician, which specifies clearly the special characteristics of the product and the rationale for not using a generally available product. The regulation on hTEPs must address this issue.

2. Two Tier Authorisation Procedure

The industry acknowledges that there will be an option under the new Regulation to follow a Centralised route for a marketing authorisation application with respect to both autologous and allogeneic products. The marketing authorisation obtained through this centralised route, including a scientific evaluation by a specific TEP committee and rules specifically adapted to these products (like fast track approval system & fee adaptations), is valid for the entire European Union.

The industry sees no reason to differentiate between autologous and allogeneic products with respect to national applications. Accordingly, the industry proposes that the Commission should allow, under the new Regulation, national applications to be made and determined for both autologous and allogeneic products.

Products should be authorised at national level using the same rules as for products authorised at Community level. The approval shall be granted through the evaluation made by a centre of excellence (see below) and under the responsibility of the Member State(s) who recognize the centre of excellence.

Products authorised at national level can only be marketed/distributed in the Member State(s) which approved it.

Manufacturers can ask the Centre of Excellence to forward its conclusions to either

- the Commission, for pan-European approval; or
- other Member States, for their individual national approval

3. Involvement of Centres of Excellence/Grouping experts

The Commission has declared that a Committee would be established at the EMEA to carry out the scientific evaluation of Centralised applications for hTEPs. It is understood that such a Committee would be comprised of Member State Experts who would act as rapporteurs/co-rapporteurs for applications made under the Centralised procedure. Thus, there would be a strong Member State contribution to the scientific assessment standards of the Community Expert Committee, which is key in view of the scarcely available expertise.

A further suggestion would be that Member States should be able to appoint their own specialised expert groups – Centres of Excellence (CoEs) to advise the Member State Competent Authorities on the compliance of a product with the standards of quality, safety and effectiveness established by the Commission and the Community Expert Committee. CoEs appointed by Member States should not be independent bodies but rather part of the structure of the Regulatory Authorities who appoint them.

The appointment of Centres of Excellence could be made as soon as practically and economically possible and as appropriate by individual Member States. The Centres of Excellence would adjudicate on the compliance of both autologous and allogeneic products, for that Member State or for and on behalf of another Member State should another Member State nominate such Centre of Excellence. The Commission and the Member States will ensure that the operation, expertise and standards of Centres of Excellence are identical to the ones required for the EMEA.

The Community Expert Committee for the Scientific Evaluation of Centralised Applications for hTEPs would be the body for providing advice to the Commission for the issue of a marketing authorisation at a Community level.

The Community Expert Committee may also have within its jurisdiction the ability to delegate the scientific evaluation for a Centralised application to a regional,Centre of Excellence, provided that the regional Centre of Excellence is subject to validation of the standards of evaluation required by the Community Expert Committee.

Any Member State may be free to nominate and/or recognise any CoE within the EU, provided that the responsibility for issuing, maintaining or revoking the accreditation of the CoE is held by that Member State or by the Commission in the case of a Centralised application.

The responsibility for the issue of marketing authorisations on the national basis would be the Member State Competent Authority irrespective of where the CoE is based and, via the Centralised route, the European Commission.

4. Relevance of Clinical Trial Directive 2001/20/EC

Industry asks the Commission to incorporate in the hTEP legislative proposal, provisions relating to clinical trial authorisations and ethics committee approvals, thus clarifying the procedure to follow and including timelines. These will be supplemented by detailed requirements to be adopted by the Commission on the basis of feedback received from

industry. This will provide legal certainty with regard to the conduct of clinical studies involving hTEPs.

In the following section, the group focused on the parts of the recently introduced Directive 2001/20/EC ("Clinical Trial Directive, CTDir") which would not be fully applicable for hTEPs because of their specific characteristics and requirements.

NB: Proposed amendments to (articles of) the Directive are in italic in the text

4.1. General Comments

There is general agreement that the regulatory framework for hTEPs should be harmonized across Europe. As a consequence, the current proposal from the Commission has the format of a regulation. It would therefore be desirable to regulate the clinical development of such products through a regulation rather than a directive which has proven to miss the objective of harmonization in this area.

The broad structure, scope and the principles for the implementation of Good Clinical Practice in the conduct of clinical trials as enforced by the CTDir and already in place since the ICH E6 Guideline on Good Clinical Practice to safeguard patients'well being and the ethical conduct of clinical trials can be applied to TEPs as well. However, the group would like to specify the following general points:

- The 'supportive documentation' to be provided for the Clinical Trials application like the toxicological or pharmacological data dossier represents a major problem. This section in the CTA Guideline[1] should explicitly be written and developed for TEPs, because the existing guidelines are specific for pharmaceutical development and those are not suitable for TEPs.

- All references in the Directive referring to human Medicinal Products should be replaced by "human Tissue Engineered Products"

- Existing concepts of GMP cannot easily be adopted for tissue engineered products and respective references need to be changed or removed from the CTDir (Article 9, para 8(a); Article 13, all; Article 15, para 1), and all related guidance documents. It should be made clear that the GMP Directive is not applicable to hTEPs without modification.

- GMP production from the first batch onwards for hTEPs in exploratory trials is impossible.(certainly for Autologous products)

- In the Essential Documents the requirement of a 'certificate of analysis' could be a possible difficulty for TEPs;

4.2. Specific Comments

A. Preamble

12. Reference to GMP should be removed because the standard requirements for GMP cannot be applied to investigational products for hTEPs

B. Text of the Directive

- **Article 1 Scope**

4. The concepts of **bioequivalence and bioavailability** do not apply to TEPs.

Proposed text: '*All clinical trials shall be designed, conducted and reported in accordance with the principles of good clinical practice'*. Reference to the concepts of biosimilarity of biotechnology products should be made as, for e.g. in the existing guideline EMEA/CPMP/3097/02 Article 2 Definitions

(d) Investigational Medicinal Product: The definition does not apply to hTEPs. Proposed text:

A human tissue engineered product being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

a) **Clinical trials** modify first sentence*: …intended to discover or verify the clinical,* ~~pharmacological and/or other pharmacodynamic~~ *structural, functional effects(and/or integration) of one or more hTEPs*

k) **'ethics committee:** Proposed text: 'an independent body in a Member State, consisting of healthcare professionals and non-medical members…..…and to provide public assurance of that protection by, among others things, *having expertise in the field of tissue engineered products,* expressing an opinion….' .

- **Article 4 Clinical trials on minors**

h) **to be modified**: the ethics committee, with pediatric *expertise and expertise in the field of tissue engineered products* or after taking advice……

g) • Article 5 Clinical trials in incapacitated adults not able to give informed legal consent **to be modified:** the ethics committee, with expertise in the relevant disease and patient population *and expertise in the field of tissue engineered products* or after taking advice……

i) **Modify:** Both, minors and incapacitated adults require specific protection because of their inability to consent themselves to participation in a clinical trial. Therefore, requirements for those groups should be similar. Proposed text:

Some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able

to give informed consent or by other research methods; additionally, such research should either relate to the clinical condition the incapacitated adult suffers or be of such nature that it can only be carried out in this group of patients..

• **Article 6 Ethics committee**

2. **modify**: An ethics committee *with expertise in the area of tissue engineered products* shall give its opinion…..

3 . a) add *: the EC shall consider in particular – the stage of current scientific knowledge*

5. **valid application** process, content and procedure will need to be adapted to TEPs to be able to obtain a valid application. This guidance should be developed in parallel with the Regulation but should be preferably the work from a Work Group consisting both of MS Regulators and Industry stakeholders.

6. Single request : is good from the point of view of timing and limiting time, however in an area which is so diverse and so new as the hTEPs, **the single request could also be counterproductive** in the case it would mean that when an applicant provides extra information following the single request and then the EC judges it is still too little information, that there would no longer be any chance for consultation and the sponsor would receive a negative vote of the EC just because the information provided was too limited or not what the EC expected. For the entire area of hTEPs more interaction could/should be necessary.

7. Review of hTEP trials should be limited to 60 days. 90 days is too long and an extra 90 days in case of consultation of a committee should be removed as well. It should be possible by accepting 'early consultation' with Competent Authorities and 'general educational efforts' in the hTEP area to keep the 60 days. Reference to xenogeneic products and somatic cell therapy should be removed.

• **Article 9 Commencement of a clinical trial**

4. Remove last sentence (re xenogeneic products) because xenogeneic products are not in the scope of the planned TEP regulation.

5. Explicit written authorization for TEPs should be **removed**. Authorization should be implicit once a positive vote of an EC has been obtained.

6. Remove reference to xenogeneic products (see 9.4)

• **Article 11 Exchange of information**

2. & 3. **To be adapted:**

- **Re Valid request for authorization to MS** : see the same remarks as for EC

- The guideline covering the application package for a clinical trial[1] needs to be adapted as well as the mandatory content in the European Clinical Trial database[2, 3]. Indeed **same comments as for EC submission apply here**. And up to 1 YEAR to obtain authorization for clinical trial start for TEPs is much too long in view of the overall development timeline we try to achieve (Not 10 to 12 years as for pharmaceuticals; and not 2 to 3 years as for devices, but 5 to 6 years max. as overall development – from discovery to market). Through 'early consultation' and 'educational efforts' it should be possible to pre-empt many questions that are arising today.

- **The use or intervention of a 'Committee of Experts' involving academic personnel reviewing the clinical trial applications , should be absolutely avoided or strict confidentiality procedures embraced** (use of RED pages principle for sensitive sections of the Clinical Trial Dossier; declaration of confidentiality signed by experts; names and affiliations of experts declared to sponsor; etc…) This is critical since a clinical trial application dossier does not provide Data Protection and the product is too far in its development from Marketing Authorization, so that copiers can otherwise easily take advantage, if dossiers are copied and distributed widely over Europe without strict confidentiality rules and controls in place (for the Sponsor and Competent Authority).

• **Article 12 Suspension of the trial or infringements**

1. 3rd paragraph: Clinical trials involving implantable living material cannot be stopped easily. Therefore, this section needs to acknowledge that for hTEPs stopping of a clinical trial may not necessarily result in immediate stop of treatment with the trial medication.

• **Article 13 Manufacture and import of investigational products**

- Qualifications of the authorized person are currently based on requirements for medicinal products / chemicals. For the authorized person, specific expertise in the field of tissue engineering seems essential.

- **Sections 3(a) and (b) should be removed, section 3(c) should read as follows:**

  for investigational products manufactured in the member state concerned, in a third country or which are a comparator from a third country , and which have a market authorization, that each production batch has undergone all relevant analyses, tests or checks necessary to confirm that its quality is in accordance with the information notified pursuant to article 9(2) of this regulation.

- A Certificate of Analysis by an independent lab, or re-analysis of a batch is often impossible for e.g. an Autologous product.

- Second last paragraph: **Modify:** Detailed guidance on the elements to be taken into account when evaluating products with the object of releasing batches within the community shall be drawn up ~~pursuant to the good manufacturing practice guidelines, and in particular Annex 13 to the said guideline.~~

- The relevant guidance documents need to be adapted to eliminate reference to GMP for investigational products and to respond to the short shelf life of many hTEPs.

- The entire logistics chain needs to be validated, including transport of batches and implantation procedures. US USP specifies e.g. that the sponsor is responsible for the product until it is re-implanted in the patient.

• **Articles 22 and 23**

Should be amended as applicable to the implementation of this Regulation.

References:

1. European Commission: Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial. Revision 1 (April 2004)

2. CT 5.1: Detailed guidance on the European clinical trials database (EUDRACT Database). Amendment describing Deployment of EudraCT – Lot 1 for 1 May 2004

3. CT 5.2: Annex to CT 5.1 describing Deployment of EudraCT – Lot 1 for 1 May 2004. Core dataset

5. Quality and risk management systems for human tissue products – Requirements

5.1. Summary

The enclosed Annex "Quality and risk management systems for human tissue products – Requirements" has been prepared considering the most relevant International regulations and standards, with the intended scope of providing a comprehensive set of rules covering all aspects of the Quality and Risk Management System for hTEPs.

Since the rules governing a Quality System cannot be easily summarized in few key points without losing significance, the document contains detailed requirements in order to give a complete set of requirements that are considered relevant for this class of products.

The list of the documents analyzed and a short rationale for the choice are as follows:

- ISO 9001:2000. It constitutes the framework of the document: it was chosen because it is a flexible standard applicable to any Quality System regardless of the product/service supplied
- Current EU GMP. It is the reference set of rules for medicinal products. Also according to the analysis made by CPMP they cannot be applied as they are to hTEPs, but several relevant provisions were introduced in the document
- U.S. Good Tissue Practices. It is a document that specifically addresses the manufacture of cell and tissue products
- EN ISO 14971. Risk Management is considered fundamental in the management of hTEPs and this standard provides complete guidance on the subject. It is proposed, however, that some additional specific guidance concerning typical hazards and risks associated with hTEPs will be required to supplement the general risk management framework provided herein

5.2. Annex I (see p 11-54)