

29 April 2004

European Commission
Enterprise Directorate-General
Unit F3 - Biotechnology, Competitiveness in pharmaceuticals, cosmetics
B - 1049 Brussels

By email: entr-human-tissue@cec.eu.int

Subject: Comments on European Commission Stakeholder Consultation on the Future Regulatory Framework for Human Tissue Engineered Products

Dear Madam, Dear Sir,

Voisin Consulting is a consulting firm specialized in advising biotechnology and pharmaceutical companies in the design and implementation of their regulatory strategy. We have developed a particular interest in the recent evolution of the pharmaceutical regulations in the European Union on innovative therapies, including cell, gene and tissue engineering therapies.

Since the company was founded in 1997, Voisin Consulting has worked with a number of European biotechnology companies on the development of their cell therapy and tissue engineering products. We have often been confronted with the lack of European regulations or lack of harmonization of the existing national regulations for these products. We therefore welcome the opportunity to give in this letter our opinion on the "Proposal for Harmonized Regulatory Framework on Human Tissue Engineered Products" published by the European Commission on 6 April 2004.

Preliminary Considerations

Voisin Consulting considers the following proposed elements are positive:

- § The choice of legal instrument, i.e. fact that the proposed regulatory framework is a Regulation and not a Directive
- § The choice of regulatory authorities: the fact that both the EMEA and the national Authorities will be involved in the regulation of Tissue Engineering Products (TEPs)
- § The fact that a Clearing House Function is planned
- § The *Lex Specialis* clause which should avoid being confronted to a lack of regulations for TEPs in Europe, even for very innovative products, provided they are not xenogenic at this time.

It will be very important that the EMEA publishes specific TEP Guidelines that will be applicable in all EU Member States soon after the Regulation is published.

In addition, the proposed Regulation should include a regulatory framework for conducting clinical trials with TEPs in the European Union, possibly with a reference to the Clinical Trial Directive 2001/20/EC, or should include a framework to obtain a centralized approval for clinical trials.

Comments on the Proposed Regulation

1. Scope of the Regulation

Xenogenic TEPs

Voisin Consulting believes that the proposed Regulation should include xenogenic TEPs. We propose that the Regulation states that these products will be the subject of an amendment to the proposed TEP Regulation, and that the Regulation gives a deadline for writing this amendment. This should ensure we will not be faced with a lack of regulation for this type of products in the near future.

Borderline Products and “Clearing House Function”

It appears essential for us to clarify even further which products will be regulated under the framework of the 2001/83 Directive and under the proposed Regulation. The “Clearing House Function” devoted to the EMEA appears adequate, however, a timeframe for providing the product classification following a request should be proposed. Thirday (30) days appears reasonable. A format for the application for classification should be provided in an EMEA Guideline.

Manufacturing Authorisation

GMP requirements should refer to the Good Tissue Practice (GTP) published by the US FDA. There is a clear need for an equivalent of the GTP in the European Union. This could be published as an EMEA or an ICH Guideline.

Marketing Authorization (General)

The EMEA should be able to deliver marketing authorizations for autologous as well as allogenic TEPs. Manufacturers of autologous products should have the choice of filing their marketing authorisation application to the EMEA or to the competent authority in the Member States.

The implantation of tissues should NOT be restricted to “authorized centers by the Member States (hospital environment)”. Implantation should be restricted by using specific requirement on the Qualified Person conducting the implantation of the TEP. A Guideline should be published on the requirements for Qualified Persons authorized to conduct TEP implantation. A TEP by TEP approach could be used, based on the nature of the cells used in the TEP for example.

Timeframe for Scientific Evaluation

As we anticipate that the content of marketing authorization application (MAA) dossiers will be significantly reduced for TEPs compared to the MAA dossiers for “traditional” medicinal products, we propose that the timeframe for scientific evaluation be reduced for TEPs. A maximum of 120 seems reasonable. It is very unlikely, that a MAA dossier for TEP will be as large, particularly for the clinical data, as for a “traditional” medicinal product.

Products Already on the Market (Grandfathering)

We believe that the proposed grandfathering clause is not acceptable. Manufacturers should be required to seek authorization for all their TEPs already on the market in the European Union when the Regulation comes into force.

Requirements for Approval

We recommend that the Regulation include a Risk Analysis section in the content of the application dossier.

The proposed annex for “detailed requirements on quality safety, efficacy” should include information on the format (Table of Contents) to be used for each section. For example a customized Common Technical Document, such as the one recently published by the French authorities (AFSSaPS) would be ideal, particularly for Module 3.

For Module 3, the US FDA regulations on the content of the quality dossier for autologous cell therapy products should be considered when writing this annex for the quality section requirements. We refer to the “Guidance for the Submission of Chemistry, Manufacturing, And Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products - January, 1997”.

The European Commission should consider the feasibility of having the equivalent of a Drug Master File in the quality section, for confidentiality reasons.

We would like to stress that for us it is very important to have the choice to be able to file a marketing authorisation application dossier to the EMEA or to the competent authorities of the Member States regardless of the fact that the product is autologous or allogenic. This will be particularly important until the competent authorities are homogenised in terms of expertise in the review of TEPs Marketing Authorization Application dossiers.

Sincerely,

Voisin Consulting

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